PROSPECTIVE STUDY OF ADVERSE DRUG REACTION OF ANTI-INFECTIVE AGENTS IN PAEDIATRIC PATIENTS

Dissertation

Submitted to

The Tamil Nadu Dr. M.G. R. Medical University, Chennai.

In partial fulfillment for the award of the degree of

Master of Pharmacy

In

PHARMACY PRACTICE

By

BINO BABU

DEPARTMENT OF PHARMACY PRACTICE

ULTRA COLLEGE OF PHARMACY

4/235, COLLEGE ROAD, THASILDAR NAGAR,

MADURAI – 625020.

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DECLARATION

I hereby declare that this thesis work entitled **"PROSPECTIVE STUDY OF ADVERSE DRUG REACTION OF ANTI-INFECTIVE AGENTS IN PAEDIATRIC PATIETS"** submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai was carried out by me in the Department of Pharmacy Practice,Ultra College of Pharmacy, Madurai under the valuable and efficient guidance of **Mr.T.Regupathi, M.Pharm,MLM.,M.B.A.,** Professor,Head of the Department,Department of Pharmacy Practice, Ultra College of Pharmacy, Madurai during the academic year Dec 2012-Oct 2013. I also declare that the matter embodied in it is a genuine work and the same has not to formed the basis for the award of any degree, diploma, associateship, fellowship of any other university or institution.

PLACE: MADURAI (**Reg. No: 26113483)**

DATE:

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CERTIFICATE

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EXAMINERS:

1.

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ACKNOWLEDGEMENT

Apart from my efforts, the success of this project depends largely on the encouragement and guidelines of many others. I take the privilege and pleasure to express my gratitude to the people who have been instrumental in the successful completion of this project.

I express my extreme sense of gratitude and profound thanks to my guide **Mr.T.Regupathi,M.Pharm,MLM,MBA**, Professor&Head, Department of Pharmacy practice, Ultra college of pharmacy, Madurai for his precious guidance, encouragement, abundant help, inspiring discussions and timely suggestions which proved for the success of this work.

I express my special thanks to **Dr.K.G SUBHASH,MBBS,BHMS,DCH** Department of Paediatrics,who had taken the pain to provide me with all the essential facilities for the completion of my project and has been a constant source of inspiration.

I do feel highly elated in manifesting a sense of gratitude to my honorable Chairman **Prof. K.R Arumugam,M.Pharm,** who permitted me to do this project and showered his blessings and guidance whole heartily in every walk of our successful careers.

It is my privilege and honour to extend my profound gratitude and express my indebtedness to our Dean **Dr.C.Vijaya. M.Pharm.Ph.D**, Ultra college of pharmacy,Madurai for her constant inspiration, valuable advice, help, encouragement and innovative ideas throughout the course of the project.

I wish to thank with pleasure and gratitude **Mr.S.KSathish, M.Pharm**, Department of pharmacy practice, Ultra college of pharmacy,Madurai for her valuable suggestions and support for the fulfilment of my dissertation.

I sincerely extend my thanks to the Librarian **Mr.P.Sankar,BA(Lit),M.L.I.Sc Miss.Sundharavalli,M.L.I.Sc** all the Laboratory staffs in Ultra College of Pharmacy.

I extend my sincere thanks to my classmates **Mr. DalvinPoulose,Mr.Jobu Kuruvilla Mr.Prashanth, Mr.Jacob Varghese,Miss.Sonia.C.George, Miss.Surya Surendran, Mr.Menge Dennis Mengate.**who helped me throughout this project.

I am very much grateful to friends in Pharmaceutics Department especially **Mr.Deepu Thomas kurien, Mr.Ratheesh G, and Mr.Vishnu Prasad** and grateful to all my seniors.

I am extremely debtful to the shadow of Lord i.e**My Parents(Mr.Babu Varghese, Mrs.LeelammaBabu) and my beloved all family members** for always standing behind me throughout the crests and troughs in journey of me and provoked me to successfully reach the destination of my project.

I whole heartedly thank all those who have stretched their helping hands towards me directly and indirectly for successful completion of this dissertation.

ABBREVIATIONS

SL.NO	ABBREVIATION	DESCRIPTION
1	WHO	World Health Organization
2	FDA	Food and Drug Administration
3	CGHS	Central Governmental Health Scheme
4	JCAHO	Joint Commission on the Accreditation of Healthcare Organization
5	ASHP	American society of Hospital Pharmacists
6	G6PD	Glucose-6-Phosphate dehydrogenase
7	CSM	The Committee on safety of medicines
8	ADROIT	Adverse drug reaction On-line Information Tracking facility
9	PMR_S	Patient Medication Records
10	EMR	Electronic Medical Record

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INTRODUCTION

ADVERSE DRUG REACTIONS

In its simple definition an ADR is any undesirable effect of drug beyond its anticipated therapeutics occurring during clinical use. The WHO defines an ADR as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis diagnosis or therapy of disease, or for the modification of physiologic function". Thus this definition excludes overdose [either accidental or intentional], drug abuse, and treatment failure and drug administration errors.[1]

Adverse reactions are recognized hazards of drug therapy. ADR's are important causes of mortality and morbidity in both hospitalized and ambulatory patients. In many countries ADR's rank among the top ten leading causes of mortality. So there is a need to study ADR's seriously to create awareness about ADR among patients to motivate health care professionals in the hospital to report ADR's to minimize the risks. Early detection, evaluation and monitoring of ADR are essential to reduce harm to patients and thus improve public health [2].

The safety of drug prescribing has become a highly visible topic in adult medicine, due in part to research suggesting that these are important ADRs caused by commonly used medications. Much less attention has been focused on neonates, infants, children and adolescents. To date, almost all investigations of ADRs have been performed in adult populations. There is recent evidence that potential ADRs may be more common in paediatirics, suggesting that the epidemiologic characteristic of medication errors may be different between children and adults.[7]

The use of medicines in children is an area of increasing interest. Infancy and childhood is a period of rapid growth and development. The varies organs, body system and enzymes that handle drugs develop at deferent rates and present a challenge to paediatrician, since drug dosage, formulations, response to drugs and adverse drug reaction vary through out childhood. Clinicians need to ensure not only that toxicity is kept to a minimum but also that children are not denied the use of appropriate medicines. Drug use in children may be accompanied by problems not seen in adults, or cause adverse drug reactions that are more frequent than in adults. [8]

An example of this is metoclopramide, which causes dystonia in teenagers and Parkinsonism in the elderly.

Paediatric patient constitute a vulnerable group with regard to rational drug prescribing. Since many new drugs are released in to the market without the benefit of even limited experience in this age group. This deficiency causes paediatricians to often prescribe children drugs in an "off – label" manner, thereby increasing the risk of drug toxicity[7].

Drug toxicity is a major limitation in providing healthcare to patients at a global level. It affects the patient's recovery as well the economy of healthcare. With the increase in production of various pharmaceutical products, newer drugs are being introduced every year. Hence, the need for an active surveillance system to remove the harmful drugs that have entered the market was well realized by WHO. This has been the basis for starting the international drug monitoring programme by WHO. [3]

In 1960 food and drug administration [FDA] began to collect reports of ADR and sponsor hospital drug monitoring and in 1964 yellow card scheme was started in UK. WHO's programme for international drug monitoring was started in 1968. Initially a pilot project in 10countries with established national reporting systems for ADR's. The network has since expanded significantly as more countries world-wide developed national pharmacovigilance centres for recording of ADR's. Currently 86 countries participate in the program which is coordinated by WHO together with its collaborating centre in Uppsala,Sweden.[4]

ADRs have a considerable negative impact on both health and healthcare costs. ADR monitoring and reporting activity is in its infancy in India because significant drug use problems like availability of prescription drugs over the counter, the simultaneous practice of different systems of health care, lack of awareness of rational drug use in the community including widespread antibiotic resistance and the occurrence of drug induced illness, non- availability of prescribing guidelines, the number of drugs prescribed are high, the ever increasing number of new drugs in the market, the lack of formal system for monitoring adverse drug reactions, and the lack of restrictions on the use of a large variety of drugs in health care delivery in the private sector may result in a

higher incidence of adverse drug reactions.[5,6]

Monitoring of adverse drug reactions started in India about two decade ago (1982). Under the Chairmanship of the Drug Controller of India, five centres were established with the idea of starting a monitoring programme nationwide. Its nodal centre (National Pharmacovigilance Centre) is located in the Department of Pharmacology, All India Institute of Medical Sciences, and New Delhi. It is affiliated to WHO collaborating centre for ADR Monitoring, Uppsala, Sweden. The others are located in PGI (Chandigarh), JIPMER (Pondicheri), KGMC (Lucknow) and Seth GS Medical College (Mumbai)-special centre. It consists of three phases: the first one being monitoring of reactions in the institutes, second one in governmental bodies like Central Governmental Health Scheme (CGHS), and the third phase proposed to include general practitioners.

Most of the adverse drug reaction monitoring programs rely on physician initiated reporting (voluntary reporting) and have been partially successful. Underreporting has been the biggest challenge in the voluntary reporting method and several reasons like increase in workload, perception that reporting will not result in any improvement and lack of knowledge that an adverse event has occurred and fear of exposing oneself to litigation. To overcome the problems in the voluntary reporting of adverse drug reactions, prompted spontaneous reporting is followed wherein physicians are prompted by medical residents, pharmacists or nurses to report any adverse drug reactions. This method of prompting the physicians every day is reported to increase the reporting and reducing the morbidity and mortality. Today's well trained pharmacists possesses a sound knowledge of the adverse effects of drugs including their predictability, reversibility, frequency, severity, predisposing factors and relationship to dosage and their treatment and prevention.

Less information is available regarding the epidemiology and prevention of medication errors and ADRs in paediatiric in patient settings. Children pose unique challenge to the system for ordering, dispensing, administering and monitoring medication. Since weight – based dosing is needed for virtually all drugs in paediatrics, ordering medication typically involves more calculations than for adults. Dispensing drug in paediatrics is also error – prone because pharmacists often must dilute stock solution. The

cardiovascular system of a premature baby maybe unable to cope with even a small error in the dosage of an inotropic agent[10].

Errors in calculating drug doses have long been recognized as an iatrogenic cause of morbidity and mortality. Error by a factor of 10 (the administration of a dose 10 times or 1/10 as high as appropriate) are of particular concern. There is a greater chance that an infant or a young child will receive such a dose of medication than that an adult will, because even a dose 10 times as high as the appropriate paediatric dose may represent an unsuspiciously small volume of stock solution[11].

Also to draw attention to an insidious form of medication error that can occur at the pharmacy dispensing stage, which to the best of knowledge has hitherto gone unreported: the provision of paper packets containing incorrect dosages of powder obtained from crushed tablets[16].

Many drugs used to treat children in hospital are either not licensed for used in children or are prescribed outside the terms of their product license. Use of off label drugs include diazepam rectal solution in children under 1 year (not licensed for age group), amiloride tablets in any children(formulation),or rectal injection of lorazepam for a child with an acute seizure(route). An example of unlicensed use is the preparation of a suspension from a tablet by the hospital pharmacy.

Categories of unlicensed use were modification of licensed drugs (such as crushing tablets to prepare a suspension), drugs that are licensed but the formulation is manufactured under a special license (such as liquid preparation of a drug that is licensed only in tablet form). New drugs available under a special manufacturing licensed (such as caffeine injection for apnoea of prematurity). Use of chemicals as drugs when no pharmaceutical grade preparation is available and imported drugs (drugs imported from a country where they are licensed). Off label use included use of a drug in situations not covered by the product license or summery of product characteristics that is, at a different dose or frequency in different clinical indication in different age groups, administration by an alternative route, or in a formulation not approved for use in children.

Although important advances have been made in paediatric clinical pharmacology, there is still a dearth of information on many aspects of adverse drugs reactions in children.

The risk of ADRs is increased in the neonates, especially when premature because of the enzymes involved in drug metabolism and elimination are poorly developed[8].

Adequate controlled clinical trails in children are lacking, mainly because of issues of cost and responsibility, and to regulations that frequently act as major obstacles. Moreover, until recently, the few clinical trails that had been performed involving children focused on the efficacy of drugs and rarely monitored their safety. If improvements in the safety of medical care for children are to take place, additional research quantifying the incidence of more generally occurring complication and describing epidemiology of those iatrogenic complication is required.

DEFINITION

Some of the most commonly cited definitions are:

- The WHO has defined as ADR an "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of a disease or for the modification of physiological functions."
- The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) defines an adverse drug reaction (ADR) as an undesired effect of a medication that either increases toxicity, decreases desired therapeutic effect, or both[9].
- Food and Drug Administration (FDA), for reporting purposes, categorizes a serious adverse event as one in which the patient outcome is death, life threatening (real risk of dying) hospitalization (initial or prolonged) disability (significant, persistent or permanent), congenital anomaly or required intervention to prevent permanent impairment or damage. Wills & Brown have given the definition for an ADR "an unintended, harmful or potentially harmful reaction which results from the administration of a single medicine at clinical doses.
- *American Society of Hospital Pharmacists (ASHP) defines a significant ADR as any unexpected, unintended, undesired, or excessive response to a drug that: Requires discontinuing the drug (therapeutic or diagnostic)Requires changing the drug therapy, Requires modifying the dose (except for minor dosage adjustments), Necessitates admission to a hospital, Prolongs stay in a health care

facility, Necessitates supportive treatment, Significantly complicates diagnosis, Negatively affects prognosis, or results in temporary or permanent harm, disability, or death. Consistent with this definition, an allergic reaction (an immunologic hypersensitivity, occurring as the result of unusual sensitivity to a drug) and an idiosyncratic reaction (an abnormal susceptibility to a drug that is peculiar to the individual) are also considered as ADRs.[9]

EPIDEMOLOGY:

They are a major clinical problem accounting for 2-6% of all hospital admissions. It causes significant financial burden on national health budget. ADRs are important causes of mortality and morbidity in both hospitalised and ambulatory patients. Many ADRs are due to irrational prescribing under diagnosis .More than four drugs in one prescription may lead to ADRs. 8-10% of hospital admissions may develop ADRs. Over to million serious ADRs reported yearly, one lakh deaths yearly caused due to ADRs. It adversely affects the patients quality of life. It causes patients to lose confidence in their doctors. It increases costs of patients care and may mimic disease resulting in unnecessary investigations and delay in treatment. [9,3,1]

CLASSIFICATIONS OF ADRs

There are many ways of classifying ADRs, Some of the generally used classifications are mentioned below.

1. <u>Rawlins &Thompson Classification:</u>

Type-A (Augmented): Commonest (up to 70%) – Dose dependent, severity increases with dose, preventable in most part by slow introduction of low dosages. Type A is predictable by the pharmacological mechanisms.
Eg: Hypotension by beta-blockers

Type-B (Bizarre): Rare, idiosyncratic, genetically determined, unpredictable, mechanisms are unknown, serious, can be fatal and unrelated to the dose.
Eg: Hepatitis caused by halothane

Type-C (Continuous drug use): It occurs as a result of continuous drug use. It may be irreversible, unexpected and unpredictable.
Eg: Tardive dyskinesias by antipsychotics

Type-D (Delayed): Delayed occurrence of ADRs, even after the cessation of treatment. Eg: Opthalmopathy after chloroquine.

Type-E (End of dose): Withdrawal reactions. It occurs typically with the depressant drugs. Eg: Hypertension and restlessness in opiate abstainer.

Type-F (Failure of therapy): Results from the ineffective treatment. Eg: Accelerated hypertension because of inefficient control.

2. <u>Wills and Brown Classification</u>:

Type A (Augmented): These include the common, pharmacologically predictable, dose related reactions, which improve when the medicine is withdrawn.

Type B (Bugs): These are pharmacologically predictable and they also improve when the medicine is withdrawn but they involve interaction with a microorganism.
Eg: Sugar containing medicine promoting dental caries.

Type C (Chemical): These involve irritant actions related to drug concentration. Eg: Contact dermatitis.

Type D (Delivery): These reactions are caused by the method of administration used or the nature of formulation. They improve when the medicine is withdrawn or the method of delivery changed.
Eg: Inflammation or fibrosis around implants.

Type E (Exit): These reactions are pharmacologically predictable but they begin only when the medicine is withdrawn or the dose is reduced. They improve when the medicine is reintroduced.
Eg: Well established withdrawal reactions with opioids, benzodiazepines.

Type F (Familial): These reactions occur only in susceptible individuals with genetically determined, inherited, metabolic disorders. They improve when the medicine is withdrawn.

Eg: Patients suffering from G6PD deficiency may experience hemolysis when exposed to quinine.

Type G (Genotoxicity): A number of drugs can produce irreversible genetic damage in humans. Notably some are potentially carcinogenic or genotoxic. Some teratogenic agents damage genetic material with in the foetus.

Eg: Metronidazole

Type H (Hypersensitivity): These reactions require activation of immune system. They improve when the medicine is withdrawn.

Eg: Anaphylaxis, Allergic skin rashes

Type U (Unclassified): Some reactions are produced by mechanisms, which are still not understood, and these must remain unclassified until more is known about them.

Eg: Metronidazole induced taste disturbance, Muscular adverse effects of simvastatin[10].

3. <u>Immunologic and Nonimmunologic Drug Reactions</u>:

Drug reactions can be classified into immunologic and nonimmunologic etiologies. The majority (75 to 80 percent) of ADRs are caused by predictable, nonimmunologic effects. The remaining 20 to 25 percent of adverse drug events are caused by unpredictable effects that may or may not be immune mediated.

Immunologic:

<u>Type</u>

Type I reaction (IgE-mediated) Eg Anaphylaxis from *b*-lactam Antibiotic

Type II reaction (cytotoxic) - Hemolytic anaemia from Penicillin

Type III reaction (immune complex) - Serum sickness from anti- thymocyte globulin.

Type IV reaction (delayed, cell-mediated) - Contact dermatitis from topical antihistamine

Nonimmunologic: Predictable

Pharmacologic side effect - Dry mouth from antihistamines

Secondary pharmacologic side effect - Thrush while taking antibiotics

Drug toxicity - Hepatotoxicity from methotrexate

Drug-drug interactions - Seizure from Theophylline while taking erythromycin

Drug overdose - Seizure from excessive lidocaine.

Unpredictable

Pseudo allergic - Anaphylactoid reaction after radiocontrast media

Idiosyncratic - Hemolytic anemia in a patient with G6PD deficiency after primaquine therapy

Intolerance - Tinnitus after a single, small dose of Aspirin

4. Gell and Coombs Classification of Drug Hypersensitivity Reactions:

The Gell and Coombs classification system describes the predominant immune mechanisms that lead to clinical symptoms of drug hypersensitivity.

Type I (IgE-mediated): The timing of reactions is minutes to hours after drug exposure.

Mechanism - Drug-IgE complex binding to mast cells with release of Histamine, mediators.

Clinical manifestations - Utricaria, angioedema, bronchospasm, inflammatory pruritus, vomiting, diarrhoea, anaphylaxis.

Type II (cytotoxic): The timing of reactions is variable.

Mechanism - Specific IgG or IgM antibodies directed at drug-hapten coated cells. *Clinical manifestations* - Hemolytic anaemia, neutropenia, thrombocytopenia. **Type III (immune complex):** Reaction occurs 1 to 3 weeks after drug exposure.

Mechanism - Tissue deposition of drug-antibody complexes with complement activation and inflammation.

Clinical manifestations - Serum sickness, fever, rash, arthralgia, urticaria, Lymphadenopathy, glomerulonephritis, and vasculitis.

Type IV (delayed, cell-mediated): Reaction occurs 2 to 7 days after cutaneous drug exposure.

Mechanism - MHC presentation of drug molecules to T cells with cytokine and Inflammatory mediators release.

Clinical manifestations - Allergic contact dermatitis, Maculopapular drug rash.

PREDISPOSING FACTORS

Three major determinants to drug response; the drug itself, the patient and the extrinsic factors. Factors related to these determinants serve as criteria for selective clinical monitoring of patients as they often predispose the patient to adverse drug reactions.

1. Drug related factors

a. **Dose:** Ingestion of excessive amounts of a drug will cause a more intense pharmacological response and a greater likelihood of adverse effects. Eg: Patients with herpes genitalis will overuse acyclovir which apart from adverse effects may even lead to drug resistance.

b. **Formulation:** Particle size, tablet disintegration time and dissolution rate, presence of excipients in dosage form and degree of purity influence drug absorption and thus the potential for adverse effects. The macro crystals of Nitrofurantoin are associated with less gastrointestinal adverse effects than microcrystalline formulation.

c. **Physicochemical properties:** Physiocochemical properties including pH, degree of ionization, lipid solubility, protein binding and extent of first pass metabolism can alter the bioavailability of a drug. A highly lipid soluble beta blocker propranolol appears to have a greater incidence of central nervous system effects relative to less lipid soluble compound like nadolol, atenolol or timolol.

d. **Rate and route of administration:** The route of administration of a drug will influence its bioavailability. The I.V route provides for complete bioavailability while the I.M and rectal routes have slower and more erratic absorption patterns. The bioavailability from oral route will depend on such factors as stability of a drug in GI fluids, extent of first pass metabolism and other physicochemical properties. There is the possibility of increased cardio toxicity with a single IV bolus injection

of doxorubicin as compared to continuous infusion, and there exists an increased incidence of nephrotoxicity with faster infusion rates of cisplatin as compared to slower rates.

2. Patient related factors a) Age

i. **Geriatrics:** Patients above 60 years of age are more likely to develop adverse drug reactions and may even need hospitalization due to adverse drug reactions. Reasons may be due to polypharmacy, poor compliance, concurrent medical illness, and alterations in pharmacokinetic and pharmacodynamic parameters. For example, the elderly have an increased incidence of digoxin toxicity because of impaired renal function, cardiovascular disease and electrolyte imbalance.

ii. **Paediatrics:** Incompletely developed intrinsic defence mechanisms predispose infants and neonates to infections and risks such as kernicterus or haemolytic anemia with sulfonamides and hearing loss with amino glycosides. Developmental bone growth can be retarded with the use of tetracyclines and corticosteroids in children younger than eight years of age. Percutaneous absorption of drugs is significantly enhanced in infants and children. Topical use of aminoglycoside-polymyxin sprays in young children has lead to permanent hearing loss and hexachlorophene sprays in neonates has caused neurotoxic related to increased absorption.

b) Gender: A higher incidence and more hospital admissions due to adverse drug reactions have been documented for women compared to men. Possible reasons for the increased adverse drug reactions include the observations that women take more drugs than men, differences in perceptions of ADRs, pharmacology of ADRs, differences in kinetics such as volume of distribution leading to gender associated differences in drug exposure, polypharmacy and hormonal differences between men and women. Chloramphenicol induced aplastic anemia and phenyl butazone induced agranulocytosis is twice and thrice as common, respectively in women patients.

c) Pregnancy: The use of drugs presents special problems during pregnancy leading from extension of their pharmacological effects on the fetus and neonate to extensive teratogenicity. Drugs like phenytoin, haloperidol, androgens, diethylstilbosterol, and

anticancer drugs like cytarabine and methotrexate have been associated with marked tertogenic effects.

d) Concurrent diseases

i. Hepatic disease: Liver failure can alter the action of any drug that depends on the normal function of the liver for its metabolism. Impaired hepatic metabolism can precipitate hepaticcoma with barbiturates or morphine, mental confusion and convulsions with cimetidine and seizures with lidocaine or theophylline.

ii. Renal disease: Renal failure increases the incidence of adverse drug reactions especially for drugs, which depend on the kidney for their elimination. Delayed renal excretion is responsible for enhanced toxicity of drugs like allopurinol, amino glycosides, digoxin, etc.

e) Genetics: Hereditary factors have been shown to predispose individuals to increased toxicity to drugs such as succinylcholine, isoniazid, monoamine oxidase inhibitors, hydralazine and procainamide. Patients with deficiency of Glucose-6-phosphate dehydrogenase (G6PD) enzyme may develop hemolytic anemia on exposure to oxidant drugs such as dapsone, sulfapyridine, primaquine and nitrofurantoin.

f) Nutrition: The nutritional status of a patient is another factor predisposing to adverse drug reactions. Monoamine oxidase inhibitors with foods rich in tyramine e.g. aged cheese and aged wines to cause hypertensive crisis with intracranial bleeding. Another drug-nutrient interaction is related to the sodium, potassium and alcohol content of drugs. Salt substitute containing potassium can cause hyperkalemia in the presence of potassium sparing diuretics, e.g. spironolactone.

3. Extrinsic factors

Environmental temperature has been cited as a predisposing factor to adverse drug reactions. Drug with significant anticholinergic activity e.g., atropine, antipsychotics and tricyclic antidepressants have precipitated heat strokes in persons exposed to hot temperature and high humidity climates. Diuretics such as thiazide may also cause

photosensitivity and even excessive loss of fluid and salt, which has negative implications for persons in hot environment.

4. Multiple drug therapy

Incidence of ADRs increase exponentially with the number of drugs prescribed and consumed indicating that the effects of multiple drugs are not always additive and safe. High prescribing rates are usually associated with the severity of disease and seriously ill patients are often predisposed to certain drug reactions. Other factors like drug interactions may also be responsible for the symptoms attributed to adverse drug reactions.[12,9]

ADR IN PAEDIATRICS

A wide range of drugs has been reported as being involved in ADR's in children. This include antibiotics NSAIDS, opiates, tuberculostatics, immunosuppressive agents, anticonvulsants etc. Incompletely developed intrinsic defense mechanisms predispose infants and neonates to infections and risks such as kernicterus or haemolytic anemia with sulphonamides and hearing loss with amino glycosides. Developmental bone growth can be retarded with the use of tetracyclines and corticosteroids in children younger than 8 years of age. Percutaneous absorption of drugs is significantly enhanced in infants and children. Topical use amino glycoside- polymyxin sprays in young children has lead to permanent hearing loss and hexachlorophene sprays in neonates has caused neuro toxic related to increased absorption.[12]

ADR's has been reported to occur frequently in children but not as frequently as in adults. Infants and very young children are at high risk of developing adverse drug reactions than adults because their capacity to metabolize drugs is not fully developed. For example new born cannot metabolize and eliminate the antibiotic chloramphenicol, new born who are given the drug may develop grey baby syndrome, a serious and often fatal reaction. If tetracyclin another antibiotic is given to infants and young children during the period when their teeth are being formed [upto about age 8 years] it may permanently discolour tooth enamel.

There are few publications among paediatric patients, though ADR incidence is usually stated to be higher in paediatric population. ADR's may adversely effects patients quality of life. It increases costs of patient care and may mimic disease resulting unnecessary investigation and delay treatment.

PROCEDURE FOR REPORTING ADVERSE DRUG REACTION

1. WHAT TO REPORT

Any undesirable adverse event suspected to be associated with use of drug; biological (including blood products), herbal drugs, cosmetics or medical devices should be reported. They should include;

1. All ADRs as a result of prescription and non-prescription.
2. All suspected adverse drug reactions regardless of whether or not the product was used in accordance with the product information provided by the company marketing the product.
3. Unexpected reaction, regardless of their nature or severity, whether not consistent with product information or labelling.
4. An observed increase in frequency of a given reaction.
5. A serious reaction, whether expected or not.
6. All suspected ADRs associated with drug-drug, drug-food or drug-food supplements interactions.
7. ADRs in special field of interest such as drug abuse and drug use in pregnancy and during lactation.
8. ADRs occurring from overdose or medication error.
9. Unusual lack of efficacy or when suspected pharmaceutical defects are observe

2. INFORMATIONS REQUIRED FOR AN ADR CASE REPORT

The minimal standard information to be provided for proper assessment of the ADR case report are;

1. Patient information
2. Adverse reactions description (include laboratory results if available)
3. Information related to the suspected drug(s)
4. Information on management of the adverse reactions
5. Information about the reporter

I. Patient information

1. Patient identity*:* indicate initials or record number of the patient in hospital, medical institution, dispensary, clinic or pharmacy.
2. Birth dates or age: indicate date, month and year
3. Sex: Male or Female
4. Weight: should be in Kilograms.

II. Adverse reaction(s)

1. Brief description of the ADR(s): Indicate the adverse(s) reaction by marking X in the appropriate box. Preferably describe briefly the nature of the adverse reaction being reported but as clearly as possible, including the body site and severity.
2. Time/date of onset of the adverse reactions*:* State the time of onset or the occurrence of the adverse reaction in relation to the administration of the drug. Indicate the date of onset in the following order; day, month and year.
3. Other relevant information*:* Patient medical history or laboratory data including dates if available, considered relevant to the case or the adverse reaction being reported should be entered. Mention appropriate laboratory tests done to the patient and results to confirm the adverse reaction. State this concisely but clearly.

III. Suspected drug(s)

1. Name of the suspected drug (s*):* trade name should preferably be used, if trade name not available, generic name may be used. Strength of the drug (s) should be stated
2. Dosage, frequency and route of administration should be clearly notified. For example;
    1. Dosage (specify dosage form; tablet, capsules, syrup, injection,cream, eye drops, etc. including total amount of drugs).
    2. Frequency: specify unit first i.e. mg, ml, mg/kg and number of time given e.g. 4 times daily or q.i.d.
    3. Route of administration by which the drug was administered.
    4. Therapy date*:* the dates of beginning and termination of the administration of each drug should be stated, and preferably recorded as follows:- date,

month and year

5. Batch number and expiry date: provide these information if available.
6. Reason for use*:* state indication or condition for which the drug(s) was given for.
7. Particular of concurrently drugs(or other treatment*)*: state particulars of other drug (s) administered by the patient concurrently with the suspected drug, including drug administration for at least 1 month back with dosage, route of administration, duration of administration and indications.
8. Provide relevant information on medical devices

3. HOW TO RECOGNISE ADRs

Since ADRs may act through the same physiological and pathological pathways as different diseases, they are difficult and some-times impossible to distinguish. However, the following steps-wise approach may be helpful in assessing possible drug-related ADRs.

1. Ensure that the medicine ordered is the medicine received and actually taken by the patient at the dose advised;
2. Verify that the onset of the suspected ADR was after the drug was taken, not before and discuss carefully the observation made by the patient;
3. Determine the time interval between the beginning of drug treatment and the onset of the event.
4. Evaluate the suspected ADR after discontinuing the drugs or reducing the dose and monitor the patient‟s status. If appropriate restart the drug treatment and monitor recurrence of any adverse events.
5. Analyse the alternative causes (other than the drug) that could on their own have caused the reaction;
6. Use relevant up to date literature and personal experience as a health professional on drugs and their ADRs and verify if there are previous conclusive reports on this reaction.
7. Report any suspected ADR to the person nominated for ADR reporting in the hospital or directly to the national ADR centre.

4. MANAGEMENT OF THE ADVERSE REACTION

1. Confirmation of the ADRs: indicate what assisted in confirming the suspected adverse reactions.

   For example:

   a) Drug reactions confirmed by disappearance of the reaction after stopping administration of the drug or reducing the doses.
   b) Recovery on withdrawal of suspected drug(s) if no other drug is withdrawn and no therapy given.
   c) Recovery follows treatment of the reaction in addition to withdrawal of drug.
2. Mention the criteria for regarding the reaction as serious.
3. Mention any treatment given to the patient after experiencing the ADRs.
4. Outcome: indicate the outcome of the adverse reaction by marking X in the appropriate box with dates in case of fatal outcome.

5. REPORTER INFORMATION

Details on reporter of an ADR: mention your particulars:-name, address of the health facility (hospital, institution, dispensary, clinic, company, pharmacy or maternity home). E-mail address (optional), signature, telephone number and date of reporting the reaction (indicate date, month and year).

6. WHO SHOULD REPORT

Reporters should bear in mind that any information related to the reporter and patient identities shall be kept confidential. The following should provide reports of any case of suspected ADRs when encountered to the patient as part of their professional responsibility:-

1. All health care professionals including specialists, doctors, dentists, pharmacists, nurses, assistant medical officers, clinical officers, pharmaceutical technicians, pharmaceutical assistants, traditional medicine practitioners and others health care providers.
2. Manufacturers or Product registrants.
3. All government hospitals, private hospitals, health centres, dispensaries private

clinics, private pharmacies and private nursing homes have obligation to report all ADR cases encountered or reported to them by the patients.

7. WHEN TO REPORT

Any suspected ADR should be reported as soon as possible. Delay in reporting will make reporting inaccurate and unreliable. If possible, report while the patient is still in the health facility this gives a chance to reporter to clear any ambiguity by re-questioning or examining the patient.

8. BASIC PRINCIPLES OF EFFICIENT REPORTING

1. Report the adverse reaction immediately after it occurs.
2. If possible, take the decision to report whilst the patient is still with you, so that the details can be filled in at once on the reporting form.
3. Think about any other factors which may contribute in causing the event such as other prescribed drugs, self-medication, herbal products, food, chemicals, ask the patient particularly about other medicines taken.
4. If you get any supplementary data later, e.g. if the same patient develops the effect again or if something happens which increases your suspicion or seem to exclude the reaction, please send in a supplementary note immediately using ADRs reporting form with the patient identifiers.
5. All reports must have the following four data elements
   i. An identifiable patient
   ii. A suspected adverse effect
   iii. A named suspected drug (s)
   iv. An identifiable reporter
6. Always write legibly. [13,14]

9. METHODS OF MONITORING ADVERSE DRUG REACTION

Although all new drugs undergo clinical trials to demonstrate efficacy and detect adverse effects, only the most common ADRs, will probably have been detected by the time the drug is marketed. In addition, clinical trials are unlikely to have been carried

out on some groups of patients, such as the elderly or pregnant women. Pharmaceutical products must therefore be monitored after marketing to identify any more unusual, serious or delayed adverse effects. Adverse event detection systems have included manual methods and combination of both electronic and manual review process.

1. Manual Methods

Manual adverse event detection systems offer the ability to detect a wide array of adverse events, and with some methods, a substantial proportion of events. The systems described below are limited by either physician reluctance to use them or the resource requirements to maintain the system

i. Provide voluntary reporting methods

a) Incident reporting

This is a cornerstone in safety initiative in the reporting and analysis of errors. Studies that have compared the rate of adverse event detection through incident reports to those detected by chart review have found that only 1.5% of adverse events and only 6% of adverse drug events are detected through incident reports. Voluntary reporting or incident reports still remain the mechanism that most institutions use to detect adverse events. [17]

Incident reports remain an attractive source of information for researchers because they are generally readily available however; problems with underreporting greatly limit their utility for patient safety research. Incident reports are underutilized because interruption in workflow, perception that completing a form will not result any improvement, lack of knowledge that an adverse event had occurred, and fear of exposing oneself to litigation.

b) Prompted spontaneous reporting

Some investigators have attempted to increase voluntary reporting through continuously prompting physicians to report errors or adverse events. Adverse events were reported through either electronic mail or paper reports. Although voluntary reporting would undoubtedly detect a broad range of adverse events, the current barriers to the

success of these systems require evaluating other methods for the detection that do not rely on physician reporting.

ii. Provider involuntary reporting methods

a) Chart Review: Most of the epidemiological evidence describing adverse medical events comes from several large studies that used chart reviews to detect adverse events. Charts undergo a two-phase screening process. Initially a trained reviewer, usually a research nurse, examine charts for screening criteria and charts with one of these screening criteria then will undergo physician‟ s review. Physician reviewers made judgments on whether they believed an adverse event had occurred based on the information contained within the chart. When a physician reviewer was more than 50% confident that medical management resulted in the injury, an adverse event was considered to have occurred. Typically, either all or a fraction of the charts are reviewed independently by two physicians. If the physician reviewers disagree on whether an adverse event occurred, the physicians will try to come to a consensus or involve a third party.

Several problems exist with this methodology. First, the positive predictive value of the initial screening process was low resulting in the physician reviewers evaluating a high number of false positive charts. Second, agreement between physicians is generally poor with respects to causality.

b) Observers: Another method used to detect adverse events has been the use of trained observers. This approach has advantages over chart review in that is can be performed prospectively. A limitation of direct observation is that it can be an expensive method for error detection. [21]

***c) Patient interviews*:** Outpatient charts are generally less data intense that inpatient charts with patient visit sometimes occurring only every few years. As a result, many researchers have relied on patient interviews to detect adverse events in these settings. Recent survey evidence suggests that patients are probably a good potential source for adverse event detection. Patient interviews offer a novel potential source for adverse event detection yet, similar to using observers, require a substantial resource commitment. Furthermore, we are unaware of any studies that have attempted to “validate” patient reports of adverse events. However, patient observations concerning their care likely

uncovers adverse events that might not be detectable by other means and the approach warrants further study.

2. Combined Modalities:

To overcome the limitations of manual methods, several electronic methods for detecting adverse events have been evaluated. Advances in information technology, the increase in hospitals with integrated information systems, and ambulatory electronic medical records now offer the ability for institutions to automatically detect adverse events. Institutions with computerized event-monitors in place have been able to detect a greater number of adverse drug events when compare to their traditional systems.

These are the methods for detecting adverse events that rely on both electronic and manual review process. In general, these systems identify an electronically stored, generally coded "signal", such as a laboratory abnormality, as screening criteria to identify charts for further review. These systems generally require fewer resources to maintain than manual systems. However, as a result of poor specificities, much of these systems still require some form of manual review.

3. The UK Yellow Card System:

1. The Committee on Safety of Medicines (CSM) superseded the Committee on Safety of Drugs after the Medicines Act in 1968. The CSM is responsible for the assessment of new drugs before clinical trials and marketing have taken place. They also manage a spontaneous reporting system, which asks doctors and, more recently, pharmacists to report all suspected reactions to new products. Doctors and pharmacists are also asked to report all serious suspected reactions to established drugs, even if it is considered that the adverse effect is well recognized. Community pharmacists are requested to focus their reporting on non-prescription medicines and both licensed and unlicensed medicinal products. In addition to the voluntary reporting of ADRs, pharmaceutical companies.
2. A system capable of capturing, retrieving and processing the Yellow Card data has been developed, known as ADROIT (Adverse drug reaction on-line information tracking facility). This database allows rapid processing and analysis of the reports to identify any potential safety issues. The Yellow Card scheme has

been successful in identifying both common and rare reactions and can also provide early warning of possible ADRs.

Some drawbacks to spontaneous reporting systems, such as this do exist:

- The incidence of a particular ADR is unknown owing to lack of information on the number of patients exposed to the drug. A rough estimate can be calculated from the number of prescriptions dispensed.
- There is considerable underreporting.
- Some bias may be introduced if there is a tendency to report ADRs, which are well publicized.
- ADRs, which are as yet unknown, are difficult to spot and so may be prone to underreporting.

4. Anecdotal reports (Case reports):

Case reports from individual clinicians are often published in the medical literature and may be important in detecting new ADRs. These single reports usually require further studies to confirm an ADR, but some serious adverse effects have been brought to light by this mechanism. Notable examples include the oculo muco cutaneous syndrome due to practolol and agranulocytosis caused by chloramphenicol.

5. Cohort studies (Prospective studies):

A „cohort" of patients taking a specified drug is identified in this type of study. They are then monitored for adverse effects. A control group is identified, which is drawn from the same population but is not taking the drug, in order to compare the incidence of adverse effects detected. It is fundamental that the two groups being compared are at equal risk of developing adverse effects, so must be of similar age, sex, overall morbidity and so on. It is also crucial to include accurate data about drug exposure, i.e. the doses used and duration.

6. Case control studies (Retrospective studies):

These studies involve a group of patients with symptoms, which it is suspected may be due to an ADR. The patients are investigated to see if they have taken the drug in question. The prevalence of drug taking is compared to that of a control group who do not have the specified symptoms. Again the two groups must be comparable and, for the association to be made with confidence, accurate information about drug exposure is required. Due to the retrospective nature of these studies, there is reliance on adequate record keeping to provide this data. If patients themselves are used as the source of information about the amount, timing and duration of drug intake, then it is important to be aware of the difficulty in recalling such information, which could lead to bias. Another key difficulty in case control studies is the need to exclude patients who are at increased risk of developing the symptoms being studied.

Despite their difficulties, these studies are useful for determining whether there is an association between a drug and adverse effect, but only once the relationship has been suspected. They cannot detect new ADRs. They are most often of value for testing hypothesis generated by spontaneous reporting.

7. Record linkage studies:

Patients medical records are used to match drugs prescribed with adverse effects experienced in record linkage studies. These studies may be particularly useful for identifying long-term adverse effects of drugs. Prescription event monitoring is an example of this type of study. This involves the identification of patients who have been exposed to a drug through dispensed prescriptions. The general practitioners with whom they are registered are then requested to submit details of all events occurring since drug exposure and details of stopping the drug if applicable. In this way events, which occur with greater than usual frequency, can be identified as potential ADRs and investigated further using case control or cohort studies.

8. Hospital-based population studies

These are useful for determining the incidence of ADRs in hospitalized patients, or on admission to hospital. Some use automatic signals from laboratory data and prescription

chart review in systematic programes. An example of this type of scheme is the Boston Collaborative Drug Surveillance Program, which involves selected hospitals in several countries. Due to the inclusion of all patients incidence rates for ADRs can be calculated and causality assessment is improved; however the studies are expensive.

9. International ADR reporting:

The World Health Organization Collaborating Centre for International Drug Monitoring was established in 1968. The centre collects spontaneous ADR reports from participating national centres and aims to increase early recognition of new and unexpected ADRs. By combining reports from many countries all over the world, very rare adverse reactions can be detected.

10. Patient-centered studies

Post marketing surveillance of medicines can be carried out using information supplied by patients. This is feasible for both prescribed and non-prescription medicines. Questionnaires are supplied to patients or telephone interviews conducted which focus on the occurrence of symptoms, which could be ADRs. Various methods can be used to identify cohorts of patients, such as patient medication records (PMRs) in community pharmacies or general practice databases. For non-prescription drugs, patients who purchase these from community pharmacies can be included in studies. These systems have been piloted in Canada, the USA and Scotland and may provide a valuable method of detecting ADRs, which complement other systems.

11. Non-prescription medicines

Since prescription medicines supplied through the NHS are recorded in medical and pharmacy records, their use can be traced and associations made with symptoms, which could be ADRs. However non-prescription medicines are obtainable from many outlets, including pharmacies, and there is no requirement for these purchases to be recorded in either medical or pharmacy records. It is good practice to include these records on PMRs when purchases are made from pharmacies and, for patients who take multiple prescription medicines; this provides a valuable source of information, which can be used to prevent ADRs arising from duplication or interactions.

Community pharmacists have an important role to play in reporting ADRs to non-prescription medicines, which are currently seriously underreported. By establishing computer records of non-prescription product purchases and therefore defining a population of users of particular products, it would be feasible to involve pharmacists in post marketing surveillance studies such as event monitoring, case control or cohort studies.

PREVENTIVE MEASURES FOR ADVERSE DRUG REACTION

Comprehensive and ongoing ADR monitoring, evaluating and reporting programs need to be initiated that should focus on the assessment of incidence, prevalence, category, severity, preventability, costs and burdens of adverse drug reactions. This will help ensure that patients receive safe medicines and mortality or morbidity due to ADRs is considerably reduced. The most ideal way to manage ADRs is to prevent its occurrence in predictable cases. However, if it has occurred, therapeutic measures become necessary.

Preventive measures are:

1. Never use any drug unless there is good indication. If the woman is pregnant do not use a drug unless the need is imperative.
2. Choose an alternative therapy of relative efficacy and safety. Eg: if patient is allergic to penicillin, choose other alternative like amoxicillin.
3. Using a prophylaxis to other drugs to prevent future ADRs. Eg: penicillin should be injected subcutaneously for skin test to prevent the occurrence of anaphylaxis.
4. Allergy and idiosyncrasy are important causes of adverse drug reactions. Ask if the person had previous reactions. There may also be family history of adverse reactions to drugs that share a common characteristic indicative of inherited disorder. (Eg: Glucose phosphate dehydrogenase deficiency).
5. Ask if the person is already taking other drugs including self medication drugs, otherwise interactions may occur.
6. Age and hepatic or renal impairment may alter the metabolism or excretion of drugs so that much smaller doses may be needed. Genetic factors may also be responsible for variations in metabolism.
7. Prescribe a few drugs as possible and give clear instructions to elderly patients or any patient likely to misunderstand complicated instructions.

8. Whenever possible use a familiar drug. New drugs are particularly alert for or unexpected events.
9. If serious adverse events are liable to occur, warn the patient.
10. Implementation of program designed to educate patient about their medication and potential for ADRs.

Documentation of ADRs is necessary to avoid re exposure[15]

REVIEW OF LITERATURE

Inocencia Martanez-Mir et al., (1999) carried out a prospective study events monitoring scheme was fused a total of 512 successive admissions to two medical paediatric wards [47 beds] were analyzed. The hospital records were screened daily during two periods [summer 105days and winter 99 days] and adverse clinical events observed were recorded. A total of 282 events were detected ; of these 112 were considered to be manifestation of ADR's. The cumulative incidence was 16.6%, no differences being observed between periods. Risk was found to be significantly higher among girls compared with boys [RR=1.66,95% CI 1.03-2.52] the gastrointestinal system was most frequently effected. The therapeutic group most commonly implicated was anti infective drugs and vaccines [49.5%]. The ADR's were mild or moderate in over 90% of cases. The consistent relationship was noted between the number of drugs administered and incidence of ADR.[18]

K.A Oshikoya et al., (2007) studied on adverse drug reaction in children found out that with prompt recognition and reporting will go a long way in minimizing the incidence of ADRs. The most commonly affected organ systems are the skin and appendages. Stevensjohns syndrome and toxic epidermal necrolysis are the most severe dermatological manifestations of ADRs. The key to appropriate management of adverse drug reactions is prevention and prompt recognition. However prevention is the best way to avert ADRs. The greatest hope lies in the future of predicting ADRs by genetic determination before drug recommendations in children[19].

Bruce C Carleton (2007) studied on adverse drug reactions in children. It was a retrospective analysis of 1193 suspected ADRs reported to Health Canada (January 1998 - May 2002). 58.6% of ADRs were for children over 13 years. 61% of reports were defined by Health Canada as serious. Case outcomes include: death (n=41) and recovered with sequelae (n=14). 4 reports of interacting drugs had fatal outcomes. Drugs most frequently cited include: isotretinoin (n=56), paroxetine (n=42), methylphenidate (n=41), amoxicillin (n=40), and valproic acid (n=32). Most frequent reaction descriptors include: psychiatric disorders (isotretinoin and paroxetine) and nervous system disorders (valproic acid, bupropion and carbamazepine). Causal links between suspected ADRs and clinical outcomes have not been established. They concluded that current ADR reporting is

insufficient to improve patient safety.[20]

Jennifer et al., (2006) Le, Pharm D studied on adverse drug reactions among Children over a 10- Year Period. It was a retrospective cohort study of paediatric patients who experienced an adverse drug reaction between January 1,1995, and December 31, 2004, was conducted at a community-based tertiary care, children's teaching hospital. They found out that a total of 1087 adverse drug reactions were reported; the overall incidence was 1.6%. The severity of most adverse drug reactions was low (levels 1–3: 89%; high levels 4–6:11%). Adverse drug reaction with low severity were significantly more common in both the general paediatric unit and the NICU.Adverse reactions resulting from use of antibiotics (particularly penicillins, cephalosporins, and vancomycin) were usually mild. In contrast, adverse drug reactions rated high in severity were significantly more common among reactions that led to hospital admission or occurred during surgery and among certain drug classes, including anticonvulsants and anti neoplastic agents. Adverse drug reaction were reported by pharmacists (89%), nurses(10%), and physicians (<1%). Although documentation of physician notification occurred for 93% of adverse drug reactions, only29% of cases were documented in the patient's medical chart,13% included follow-up education for individuals involved, and10% were updated in the allergy profile of the hospital computer system. They concluded that measures to improve detection and reporting of adverse drug reactions by all health care professionals should be undertaken, to enhance our understanding of the nature and impact of these reactions in children[21].

Seyed Bahram Mir Saeed Ghazi et al., (2007) studied the adverse Drug Reactions as a Cause for Admissions to a Children's Hospital. They aimed to investigate the adverse drug reactions (ADR) in paediatrics and determine the predominant symptoms of adverse drug reactions in children. This case series study was carried out at the Bahrami Pediatric Hospital, Tehran where the files of 25 admitted patients with the diagnosis of adverse drug reaction 1998 to 2005 were studied. The average age was 4.6 (±3.7) years and symptoms of adverse drug reactions were observed12.6 (±14.3) days after initiation of the drug intake. Skin rash was seen in all patients more in form of maculopapular rash followed by urticaria. Arthralgia was the next common symptom observed in 44%of patients. The common abnormal laboratory data was high erythrocyte sedimentation rate which was seen in 40% of patients. The most common ingested drugs were phenothiazine and sulfasalazine

(eachof them seen in 28% of patients) followed by penicillin (16%), furazolidone (16%), cephalosporins (4%) and valproic acid (4%). In 28% of patients poly-pharmacy was responsible for ADR. They concluded that awareness of the problem, observation of poly-pharmacy and potential drug-drug interactions, and continuous re-evaluation of the ongoing individual pharmacotherapy is important, especially in children, to reduce ADRs. [22]

A Circo-Begovic et al., (1989) carried out a study on intensive monitoring of Adverse drug reactions in infants and preschool children in paediatric outpatient unit covering the town of Karlovac was performed over a period of time of three months. Data were obtained by physical examination of children and the history given by their parents. In all 2359 children were examined. ADR was recorded in 63 children and were reported to the national ADR monitoring centre in Zagreb using the algorithm of Hutchinson et al [1979], all ADR were classified as "definite", "probable", "possible" and "unlikely". Drugs were prescribed in 97.3% of children, 60.24% received an anti microbial agent and an antipyretic was given to 1878 children, mostly paracetamol. ADR were most frequently caused by antibiotics[49 reactions to penicillin V, and 15 to amoxycillin] and secretolytics [7 reactions]. ADR were followed by complete recovery and not a single child was hospitalized because of ADR.[17]

Pirmohamed et al., (2004) carried out a prospective observational study over a 6-month period. 18,820 people admitted to emergency departments or acute medical or surgical units were screened for ADRs. The ADR was directly responsible for 80% of these cases (95% CI 78 to 82, n = 980). People with ADRs used 4% of hospital beds (median stay 8 days, projected annual cost to NHS of £466 m). The overall fatality rate due to an ADR was 0.15% (28/18,820 individuals). Gastrointestinal bleeding was the most common ADR. Drugs commonly causing ADRs were aspirin NSAIDs, diuretics and warfarin. Drug interactions accounted for 16.6% of ADRs. The authors concluded that adverse drug reactions account for a high number of admissions, most of which are avoidable[23].

M I Kidon, et al., (2004) conducted a study on adverse drug reactions in Singaporean children. They aimed to define the prevalence and characteristics of reported drug allergies in hospitalized children in Singapore. It is a retrospective case control study was performed through the hospital's inpatient electronic medical record (EMR) for the

period of August 2002 to December 2002. Of the 8437 patients hospitalized during the study period, reports of previous ADRs were found in the records of 222 patients. The mean age of the patients was 7.4 years, range 2 months to 17 years (95 percent confidence interval [CI] 6.3 - 8.4). There were 146 males and 160 Chinese. The most commonly- involved medications were betalactum antibiotics (45 percent) and non steroidal anti-inflammatory drug (18.5 percent). Compared to the control group, children with a reported ADR were more likely to be older, with a mean age of 7.4 years versus 4.6 years (p-value less than 0.001), male (odds ratio [OR] 1.7, 95 percent CI 1.2-2.4), of Chinese descent (OR 1.8, 95 percent CI 1.5-5), have an associated chronic illness (OR 3.5, 95 percent CI 2.5-5), and a diagnosis of asthma (OR 2.7, 95 percent CI 1.7-4.5). They concluded that in paediatric inpatient population, the risk of reported ADRs increases with age, male gender, Chinese descent and the presence of chronic disease. The major drugs involved are betalactam antibiotics and non-steroidal anti- inflammatory drugs.[24]

BA King et al., (2003) studied adverse skin and joint reactions associated with oral antibiotics in children. It was a 12 month retrospective study. To describe clinical course of children with cefaclor related serum sickness like reactions and compare these with cases reported to the ADRs advisory committee. They found out that 150 children occurs adverse skin reaction, 70 after cefaclor alone, 10 after cefaclor in combination with other antibiotics and 70 after other antibiotic courses. SSLR occurred in 44 children; 32 after cefaclor alone, 5 after cefaclor in combination with other antibiotics and 7 after other single antibiotics.In children with cefaclor SSLR, otitis media was most common indication, other had viral illnesses. Prolonged sequele in 4 children. 60 reports of paediatric cefaclor SSLR were made to ADRAS during study period and none originated from PMHED.[25]

Helene Peyriere et al., (2003) studied adverse drug events associated with hospital admissions in saint-eloi hospital. It is a prospective study of 48 days to increase the knowledge based on the frequency, causality and avoidability of ADR events as a cause for admission in internal medicine or when occurring during hospitalization. A total of 156 patients (70men and 86 women) were included. The investigators put forward their results as patients mean age SD was 66.5+_ 18.1 years and mean length of stay was 13.2 +_9 days. 38 ADEs occurred in 32 patients. In 15 cases, ADEs were identified as the reason for admission, but were not the cause of admission. The most frequent ADEs involved

neurologic (23.6), renal (15.7%) and hematologic systems. Among these ADEs, 22 were considered avoidable (57.9%); 20 of these were associated with therapeutic errors. Patients with ADEs stayed longer in the hospital and took more drugs both before and during their hospital stay. The authors concluded that most of the ADEs observed in their study were avoidable. The risk/ benefit ratio of administered drugs could be improved with better knowledge of the patients medical history and risk factors of ADEs[26].

Samuel et al., (2003) made an attempt to introduce an ADR monitoring programme at two hospitals and an outpatient skin specialty clinic in South India to evaluate the programme. They introduced an ADR monitoring programme in three participating centres and ADRs were documented and analyzed over a period of six months. In total, 152 ADRs were documented. The percentage of patients with a reported ADR at each of the three centers was 3.5, 3.7 and 2.3. Using Naranjo's probability scale, 25.7 per cent of ADRs were categorized as "probable" and 74.3 per cent as "possible". Of the ADRs reported in the two hospitals, 31.1 per cent related to unplanned medication-related hospital admissions and 68.9 per cent occurred during the hospital stay. Antibiotics (32.2 %), psychotropic drugs, steroids and non- steroidal anti-inflammatory drugs (11.8% each) were the most common drugs that caused ADRs. Occurrence of ADRs seemed to be similar to those reported in the developed world, with the exception of the proportion of severe ADRs (25%), which was higher than reported elsewhere in published studies.[26]

Jutta Weiss et al., (2012) studied ADRs in 1 ward and assessed whether a general approach, e.g. by a computerized monitoring system, to detect ADRs in children feasible and likely to yield a higher rate of early detected ADRs. The aim was to assess the usefulness of a computerized monitoring system before implementing costly adaptations .It is a 8-month prospective study was conducted at a 10-bed paediatric isolation ward of the University Hospital. A total of 68 ADRs were detected in 46 of 214 patients by the pharmaco epidemiological team. Thirty-four ADRs (50%) were detected by the staff physician, and 27 (40%) were detected primarily by analyzing laboratory parameters. Antibiotics-associated ADRs(50%) predominated, followed by glucocorticoids (16%), tuberculostatic(4%), and immunosuppressive agents (4%). In 5 cases, an ADR was responsible for the prolongation of hospital stay, and in4 children, the ADR was responsible for hospitalization. They concluded that detection rate of ADRs would almost be doubled by

a computerized monitoring system analyzing laboratory data. Implementation of a computer monitor system that automatically generates laboratory signals may help to identify ADRs in children, and to reduce morbidity and hospital stay, as well as costs.[28]

Lazarou, J et al., (2001) studied the incidence of adverse drug reactions in hospitalized patients. Their aim was to estimate the incidence of serious and fatal adverse drug reactions (ADR) in hospital patients. Four electronic databases were searched from 1966 to 1996. of 153, they selected 39 prospective studies from US hospitals. Data extracted independently by 2 investigators were analyzed by a random-effects model. The overall incidence of serious ADRs was 6.7% (95% confidence interval [CI], 5.2%-8.2%) and of fatal ADRs was 0.32% (95% Cl, 0.23%-0.41 %) of hospitalized patients. We estimated that in 1994 overall 2 216 000 (1721000-271 000) hospitalized patients had serious ADRs and 106000 (76000-137000) had fatal ADRs, making these reactions between the fourth and sixth leading cause of death. They concluded that the incidence of serious and fatal ADRs in US hospitals was found to be extremely high.[29]

Asawari L Rout et al., (20012) carried out a prospective observational study for the duration of 8 months amongst medicine inpatients of a teaching hospital. Preventability, Predictability and Seriousness were assessed for each suspectedADR. In addition to this, effect of length of stay on happening of an ADR was also assessed. Our finding showed about 34% ADRs were “Definitely preventable”, 21% were “Probably preventable”while remaining 45% were “Not preventable”. 72.71% of the reactions prolonged the hospitalization of patients whereas 25.18% of the reactions required intervention to prevent permanent damage and only 2.10% of the reactions were life threatening. Almost 69% ADRs deemed predictable. Although ADRs encountered in the study are non serious and not preventable, management of such ADRs through therapeutic interventions would be beneficial in better patient outcome[30].

Jha N et al., (2007) carried out an analytical cross sectional study designed from May 2007 to September 2007 in which prevalence of ADR was calculated. A total of 37 cases of ADRs were taken from 4287 patients and 10% of the remaining population without ADRs i.e. 425 out of 4250 patients was selected randomly. Prevalence of ADR in this study was 0.86% and male to female ratio was 0.85. 54.1% were female and 45.9% were male (P =

0.65). The highest percentage of ADRs were seen in adult patients, however the difference was statistically not significant. Maximum numbers of ADRs were reported from skin, 35.13% followed by GIT, 29.72% and then from CNS, 18.91%. Anti-infectives were associated with maximum number of ADRs followed by IV urograffin. Rashes, 35.13% were the most common type of ADRs reported followed by vomiting, 13.51% and then dizziness which was 10.81%. Regarding the outcomes attributed to ADRs, one patient died due to ADR caused by dapsone and 15 cases got hospitalized due to ADRs. For causality of ADRs, according to Naranjo algorhythm scale, 35% of reactions were assessed to be probable, 32% as possible and 19% were definite. Similarly, for severity assessment, 54% reports were mild, 35% were moderate and 10.81% were severe. Prevalence of ADR in this study was 0.8% which is similar to other studies in other countries. All the ADRs were not toxic reactions and they were unpredictable[36].

A summary analysis of three descriptive studies of significant adverse drug events (ADEs) was conducted by William. Case reports of ADEs published in Clinical Alert during 1976-97 were the source of information on ADEs. William's studies revealed that during the 21-year period, 1520 significant ADEs were reported, 29% of which resulted in death, 15% in permanent disability, and 56% in life threats. Event types were distributed as adverse drug reactions (52%), allergic drug reactions (25%), medication errors (15%), and drug interactions (8%). The drug categories most commonly involved in ADEs were central-nervous-system agents, antimicrobials, antineoplastics, and cardiovascular agents. The nervous, hematopoietic, cardiovascular, and respiratory systems were affected the most. Overall, 52% of the cases were judged to have been preventable; of these, a pharmacist could have prevented 50%.

A study conducted by G.Stavreva et al., (2011) also revealed the predominance of Cephalosporins whereas fluoroquinolones were most accounted in a study conducted by M.M Hussain et al. while Vancomycin and Penicillins were most frequent in the study of R. Priyadharsini et al.[31,32]

Palaniswami S, et al., (2009) carried out a prospective observational study for a period of 6 months in an inpatient and outpatient department of a south Indian hospital. In a total of 96 patients, nearly 59 percent of patients were male it indicates that the prevalence of

ADRs is more in men than in women. 42.71 percent (41) ADRs were found in the age group between 41 and 60 shows that ADRs in this locality hospital is more in these age group peoples. Most of the ADRs were treated by withdrawing the offending drug (81.25%). WHO probability assessment scale shows 42.71% (41) cases were probable, of which 27.08% (26) were male and 15.63% (15) were female. 5.21% (5) ADR were unclassified or in assessable. Naranjo's causality assessment scale shows 5.21% (5) of ADRs were Definite, 90.62% (87) of ADRs were probable, and 4.17% (4) of ADRs were possible. Many of the ADRs were reported from Neurology department (40.63%), it is followed by internal medicine department (20.83%) and other departments[37].

Analysis of the type of reported ADRs according to Rawlin and Thompson revealed Type A predominance. This result is in line with the study conducted by K.A Oshikoya et al and G.Starveva et al but in another study by Suthar J.V and Desai S.V, all the reported reactions were Type B reactions. Type A reactions are dose related and thus were preventable from their known pharmacology and therefore all of them were potentially avoidable. R.G Eva states that Type B reactions comprise approximately 10-15% of all ADRs and include hypersensitivity drug reactions.[33]

AIM AND OBJECTIVES

AIM AND OBJECTIVES

- To detect and analyze adverse drug reactions of anti-infective agents in children between 1-10years of age.
- To detect the incidence rate of adverse drug reactions of anti infective agents in children between 1-10years of age.
- To study the extend of incidence and severity of ADR's in our hospital.
- To assess the casualty of ADR caused by anti infective agent in childrens.

As the number of formulations available in Indian market has crossed more than 1 lakh, the process of choosing and prescribing the most suitable drug for individual patients, with lesser adverse effects is becoming increasingly complex for the physicians. Most studies of adverse reactions to drugs in children have been based on subjects who received drugs in hospital or at home shortly before admission.

As hospital drug use is very different from outpatient service, the incidence and profile of adverse reactions might also be expected to vary. Intensive monitoring of pediatric sideeffects has rarely been done. The purpose of the present study was to monitor the incidents and causes of ADR in children treated with anti-infective agents in a general pediatric inpatient unit at CGM Health care Sree Shanmughavilasam Hospital.

PLAN OF WORK

The present dissertation work was planned to determine the adverse drug reaction of anti-infective agents in paediatric patients. The work was planned to conduct in C.G.M Healthcare Sree Shanmughavilasam Hospital, Punalur .

The plan of work includes:

1. Submission of protocol for approval from Institutional ethical committee.
2. Designing data collection form.
3. Collection of case histories of the patient with cutaneous ADRs.
4. Collection of consent from patients care taker.
5. Evaluation of collected data.
6. Designing casuality assessment Naranjo Algorithm scale
7. Assessment of level of severity of ADRs using Hartwig scale.
8. Data analysis with the help of computer using Microsoft Excel 2007.

MATERIALS AND METHODS

MATERIALS AND METHODS

A prospective spontaneous reporting study involving active methods [pharmacist actively looking for suspected ADR's] and passive methods [stimulating prescribers to report suspected ADR] was carried out in a general paediatric inpatient department of C.G.M Healthcare sree shanmughavilasam Hospital, Punalur between February and July 2013. A total number of 100 paediatric patients will be included in the study. All the suspected ADR's due to anti-infective medication in paediatric inpatient aged between 1 to 10 years were noted and reported by various departments of this hospital are included in this study. Drug reactions that results due to medication errors, use of alternative systems of medicines, and departments like dentistry, surgery, oncology etc are excluded. The data for the study was taken from case sheets, investigation reports of patients who had experienced an ADR, personal interviews with patients or patient's attendant, past history of medication use, personal interviews with reporting persons or clinicians.

The causality assessment of the reported ADR's was carried out using "Naranjo causality assessment scale". The Naranjo Algorithm, the drug reaction can be classified as definite, probable, as possible. The modified Hartwig and Siegel Scale classifies severity of ADR as mild, moderate or severe with various levels according to factors like requirements for change in treatment, duration of hospital stay, and the disability produced by adverse drug reaction.

METHODOLOGY

STUDY DESIGN

It is a prospective spontaneous reporting study.

STUDY CENTRE

C.G.M Health care Sree Shanmugha vilasam Hospital,Punalur, Kollam,Kerala.

STUDY POPULATION

Paediatric in patients aged between 1-10 years treated with anti infective agents.

STUDY PERIOD

6 Months

SAMPLE SIZE

100

STUDY CRITERIA

INCLUSION CRITERIA

1) Paediatric patients, aged between 1-10 years, treated with anti infective agents
2) Both male and female paediatric inpatients treated with antibiotics, anti viral, anti fungal drugs etc. are included in the study.
3)

EXCLUSION CRITERIA

1) Drug reactions that results due to medication errors, use of alternative systems of medicines, departments like Dentistry, Oncology etc are excluded from the study.
2) Terminally ill patients.
3) Those who did not consent to be interviewed.

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3) Those who did not consent to be interviewed.

STUDY VARIABLE

ADR caused by anti infective agents in paediatric inpatients between age group 1-10 years. The suspected ADRs produced by commonly used antibiotics like ampicillin, amoxicillin, chloramphenicol, azithromycin, erythromycin, tetracycline etc. Then antiviral drug acyclovir, anti fungal drug fluconozol etc was monitored by this study.

The data for the study was taken from case sheets, treatment charts, investigation reports of patients who had experienced an ADR, personal interviews with patients or patient's attendant etc.

Analysis of the results: The data collected during the period are to be statistically analyzed for the following parameters.

- The total number of ADRs reported.
- Age groups and gender of the patients
- Assessment of causality based on ' Naranjo Scale'
- Assessment of level of severity of ADRs using 'Hart wig Scale'

RESULTS

During the study period, 12 ADRs of anti infective agents were reported. Table 1 shows the list of reported ADRs.

LIST OF ADRs REPORTED DURING THE STUDY PERIOD

Table 1

SL NO	NAME	GENDER	AGE	SUSPECTED DRUG	ADR REPORTED	REASON FOR ADMISSION
1	ISHANI	F	3 YR	AZITHROMYCIN	DIARRHOEA,EPIGASTRIC DISTRESS	BRONCHITIS
2	NUMAN	M	4.5 YR	AMOXYCILLIN	FATIGUE,ABDOMINAL PAIN,VOMOTTING	RHEUMATIC FEVER
3	ADARSH	M	3.5 YR	AMPICILIN	LOOSE STOOLS,ABDOMINAL PAIN	CHOLERA
4	ANJU	F	4 YR	CEFIXIME	DISPEPSIA,SEVERE HEAD ACHE	BRONCHITIS
5	VINDHYA	F	4 YR	AMIKACIN	DECREASED GFR	RENAL INFECTION
6	PREETHI	F	5 YR	CEFTRIAXONE	THROMBOPHLEBITIS, CANNULA SITE INFLAMMATION	MENINGITIS
7	ARUN	M	2 YR	BENZYL PENCILLIN	LOCAL IRRITATION, MILD RASH	BRONCHO PNEUMONIA
8	NIGKILA	F	4 YR	METRONIDAZOLE	EPIGASTRC DISTRESS,VOMITTING	AMEBIASIS
9	MELVIN	M	7 YR	VANCOMYCIN	MACULO PAPULAR RASHES ON FACE AND NECK	MENINGITIS
10	MIDHUN	M	5 YR	BENZYL PENCILLIN	LOCAL REACTION,HYPERSENSITIVITY	BRONCHO PNEUMONIA
11	DIVYA	F	6 YR	CIPROFLOXACIN	ITCHING,SKIN RASHES	THYPHOID FEVER
12	MANJU	F	4 YR	CLOXACILLIN	DIARRHOEA,EPIGASTRIC DISTRESS	UPPER RESPIRATORY TRACT INFECTION

TABLE : 1

TOTAL NUMBER OF ADRs DUE TO ANTI INFECTIVE AGENTS

Total number of subject (N)	**100**
Number of reported ADRs	**12**

REPORT:

Among 100 paediatric patients treated with anti infective agents, 12 ADRs were reported and the incidence rate was found to be 12%.

FIGURE : 1

TOTAL NUMBER OF ADRs DUE TO ANTI INFECTIVE AGENTS

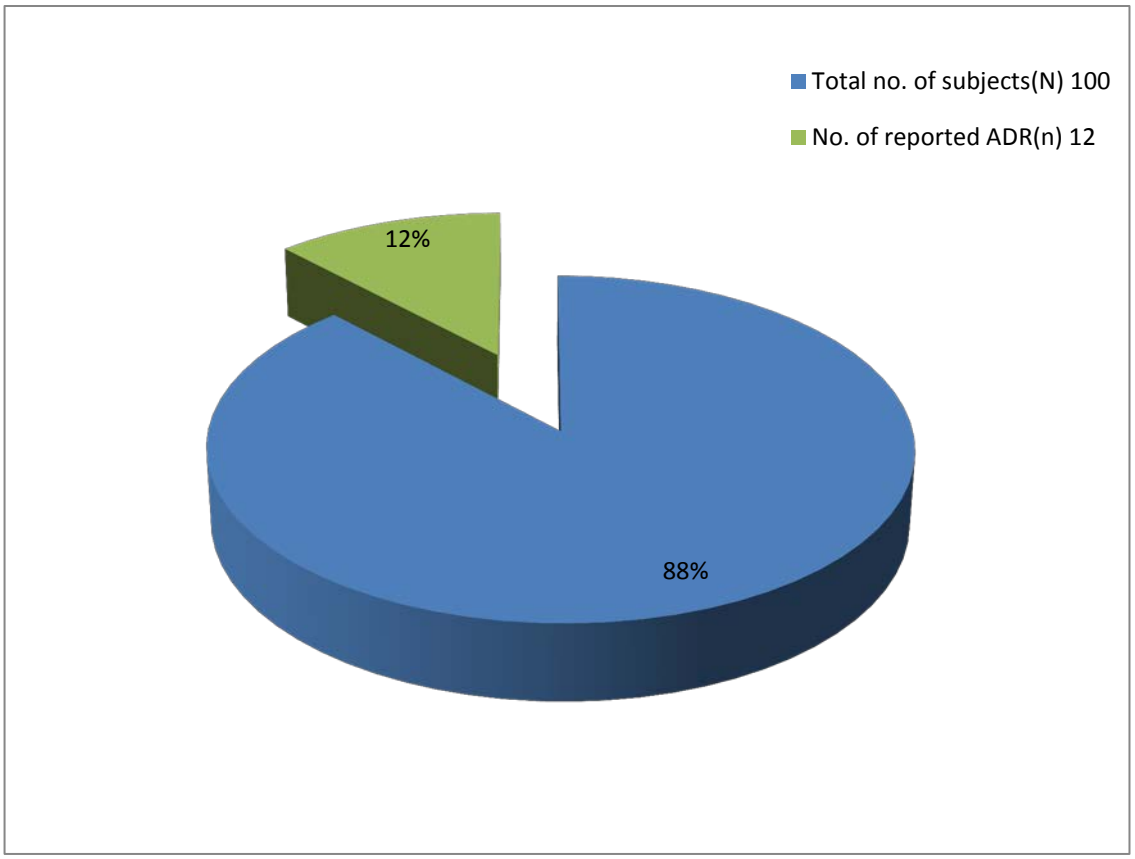


TABLE : 2

NUMBER OF ADRS REPORTED BY ACTIVE OR PASSIVE METHOD

ADRs reported by	Number	Percentage
Active method	**7**	**58.30%**
Passive method	**5**	**41.66%**

Total number of ADRs reported =12

REPORT:

Out of 12 reported ADRs ,7 (58.30%) was reported by active method and 5 (41.66%) by passive method.

FIGURE : 2

NUMBER OF ADRS REPORTED BY ACTIVE OR PASSIVE METHOD

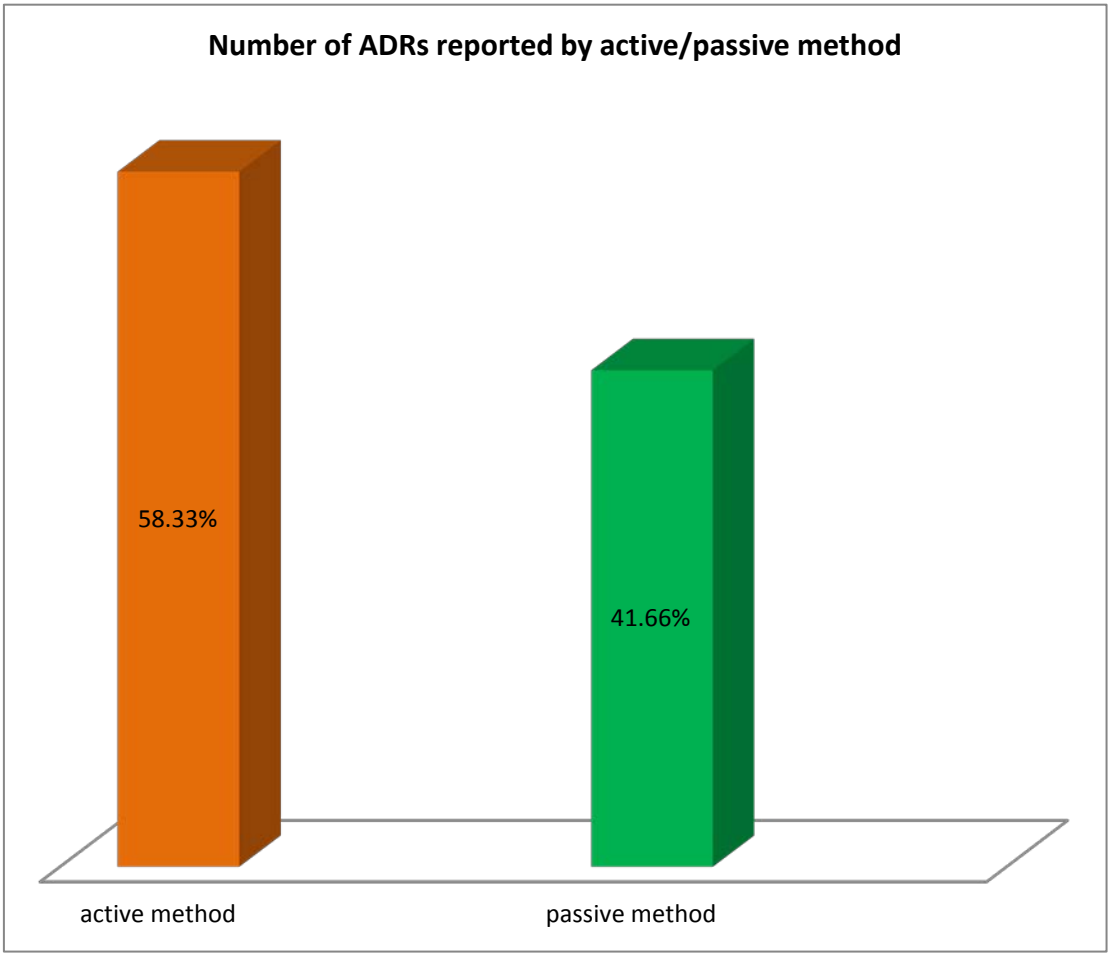


TABLE : 3

DIVISION OF ADRs BASED ON GENDER OF THE PATIENTS

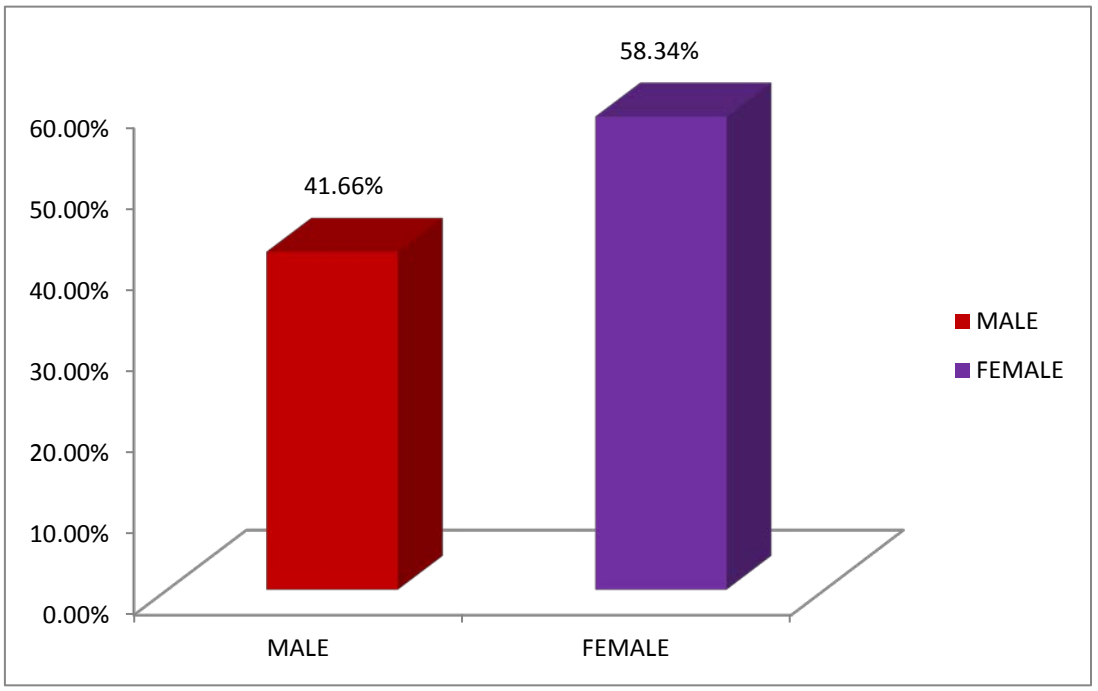
Sex	Number	Percentage
Male	**5**	**41.66%**
Female	**7**	**58.34%**

REPORT:

The incidence rate was found to be more in Females 7 (58.34%) and less in male paediatric patient 5 (41.66%).

FIGURE : 3

DIVISION OF ADRs BASED ON GENDER OF THE PATIENTS



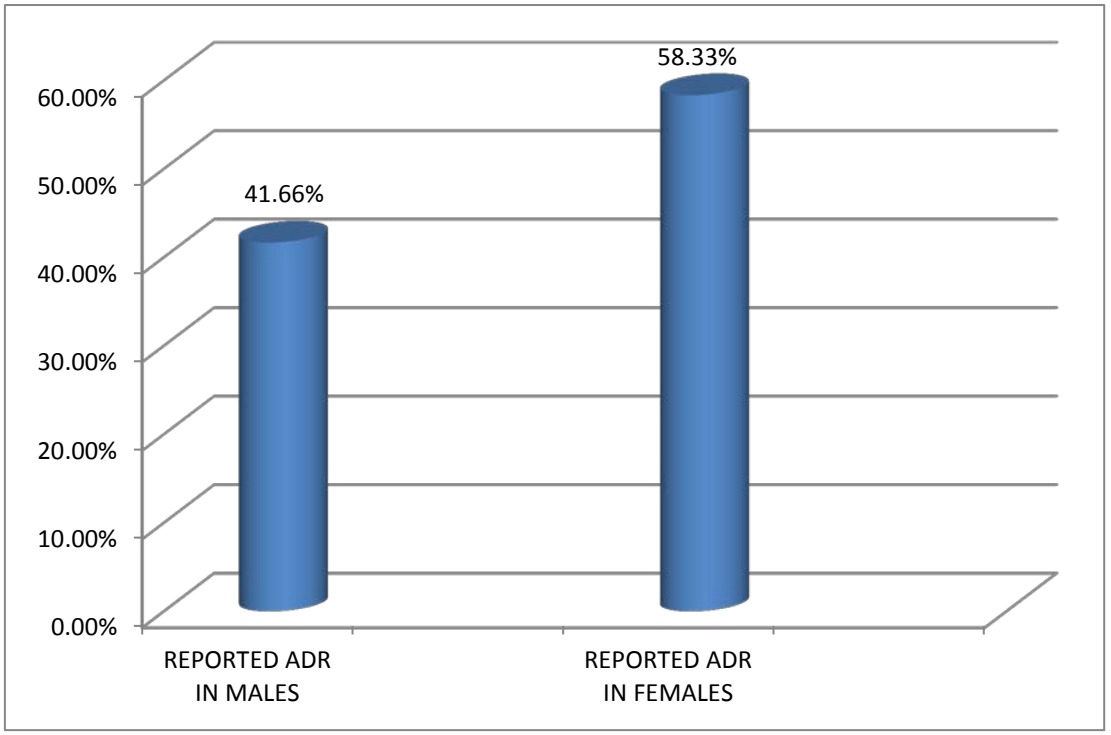


TABLE : 4

THERAPEUTIC CLASS OF ANTI INFECTIVE AGENT

Class of anti infective agents	Number	percentage
Penicillins (Ampicillin,Cloxacillin, Amoxycillin,Benzyl penicillin)	5	**41.66%**
Glycopeptide (Vancomycin)	1	**8.33%**
Cephalosporin (Cefixime,Ceftriaxone)	2	**16.66%**
Aminoglycosides (Amikacin)	1	**8.33%**
Macrolides (Azithromycin)	1	**8.33%**
Fluroquinolones (Ciprofloxacin)	1	**8.33%**
Antibnacterial/amoebicide (Metronidazole)	1	**8.33%**

REPORT:

The antibiotic class mostly affected with ADRs in paediatric inpatients was penicillins 5 (41.66%) followed by cephalaosporin 2 (16.66%) and macrolides 1(8.33%).

FIGURE : 4

THERAPEUTIC CLASS OF ANTI INFECTIVE AGENT

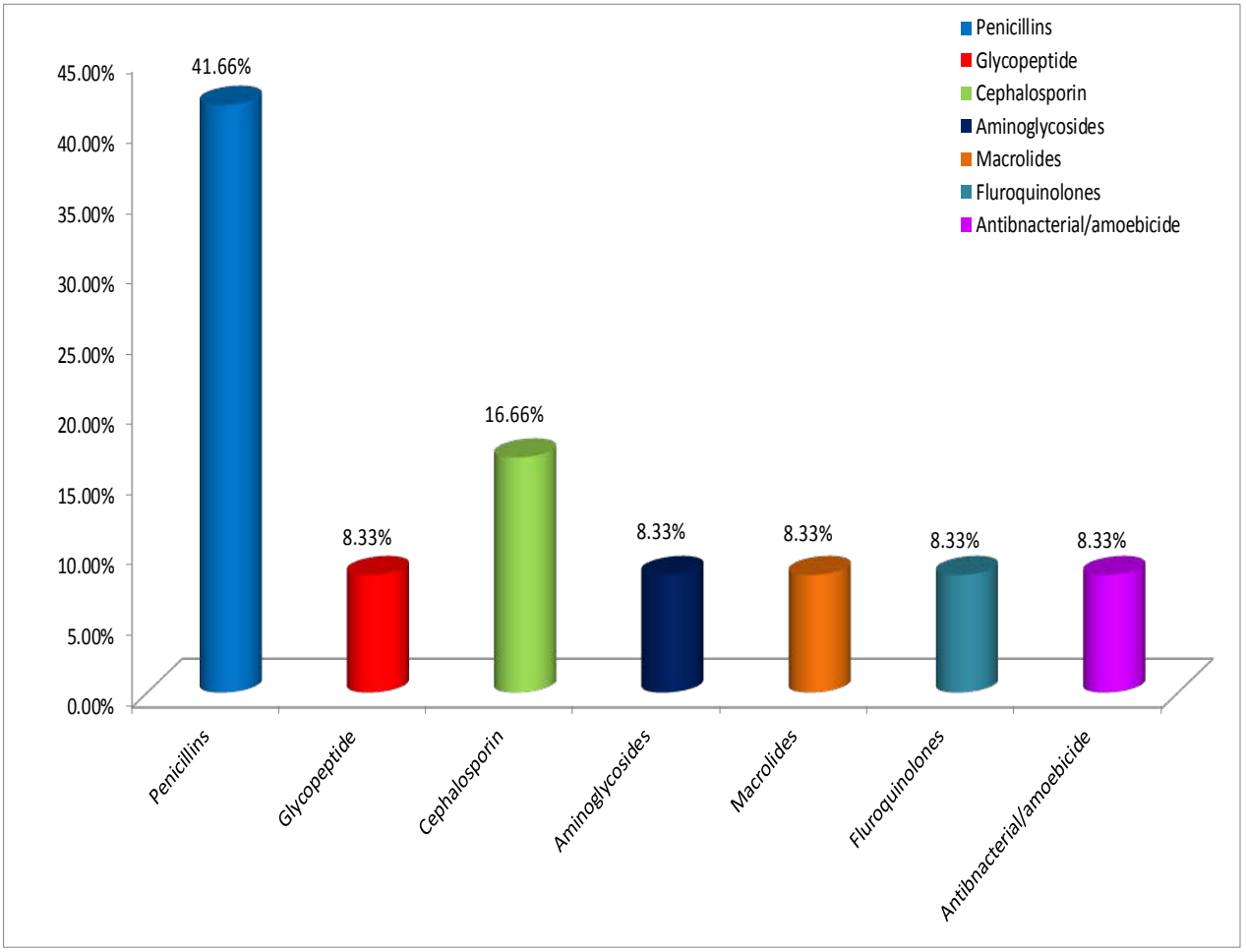


TABLE : 5

ORGAN SYSTEM AFFECTED DUE TO ADRs

Organ system	Number	Percentage
GIT	**7**	**58.33%**
Skin	**3**	**25.00%**
Nephro toxicity	**1**	**8.33%**
CNS	**0**	**0%**
Respiratory	**0**	**0%**
Haematological	**0**	**0%**
Local reaction	**1**	**8.33%**

REPORT:

Organ system most affected by ADRs due to antibiotics was found to be GIT 7 (58.33%) followed by skin 3 (25.00%) and .local reactions 1 (8.33%).

FIGURE : 5

ORGAN SYSTEM AFFECTED DUE TO ADRs

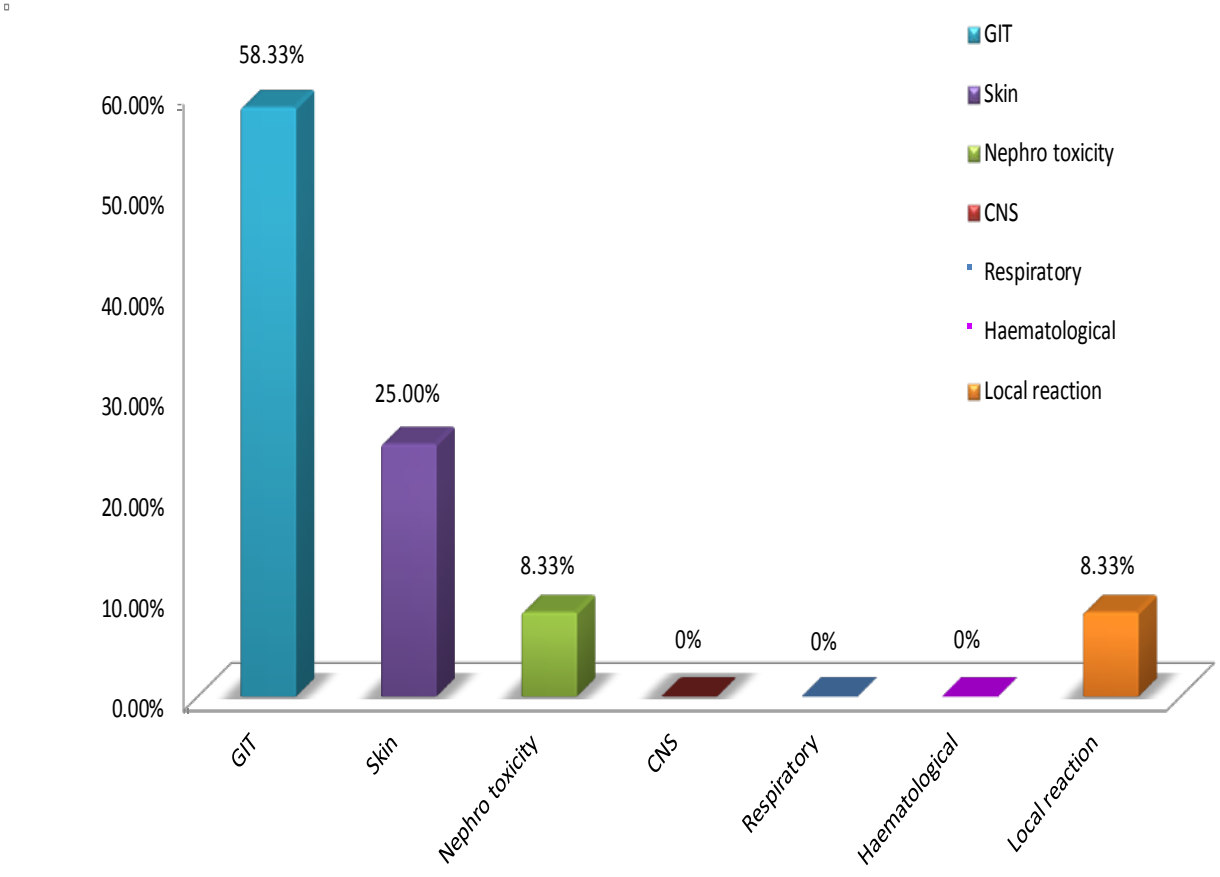


TABLE : 6

CLASSIFICATION OF ADRs

Type of ADRs	Number	Percentage
Type A	**10**	**83.33%**
Type B	**2**	**16.66%**

REPORT:

Type A reactions 10 (83.33%) was most common compared to type B 2 (16.66%).

FIGURE : 6

CLASSIFICATION OF ADRs

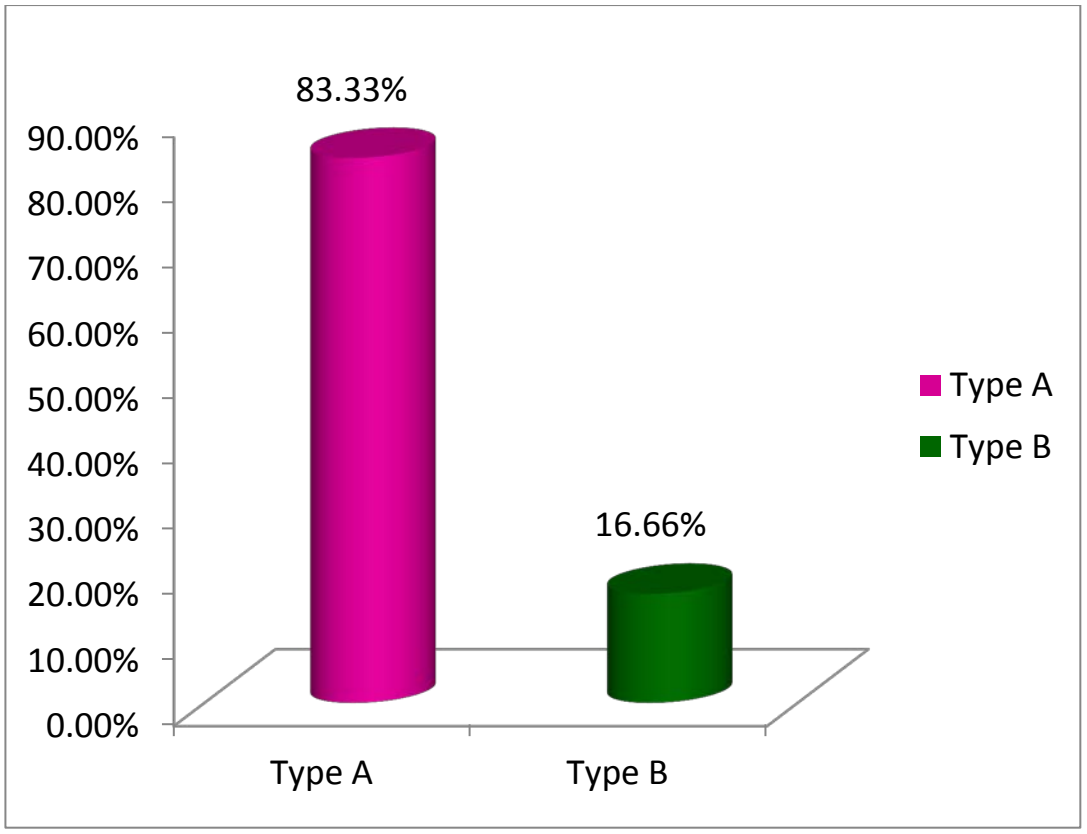


TABLE : 7

ROUTE OF ADMINISTRATION OF ANTI INFECTIVE AGENTS THAT CAUSE ADRs

ROA	Number	Percentage
Oral	6	**50.00%**
Parenteral	6	**50.00%**

REPORT:

Among 12 reported ADRs 6 (50.00%) was due to oral route of administration and 6 (50.00%) parental.

FIGURE : 7

ROUTE OF ADMINISTRATION OF ANTI INFECTIVE AGENTS THAT CAUSE ADRs

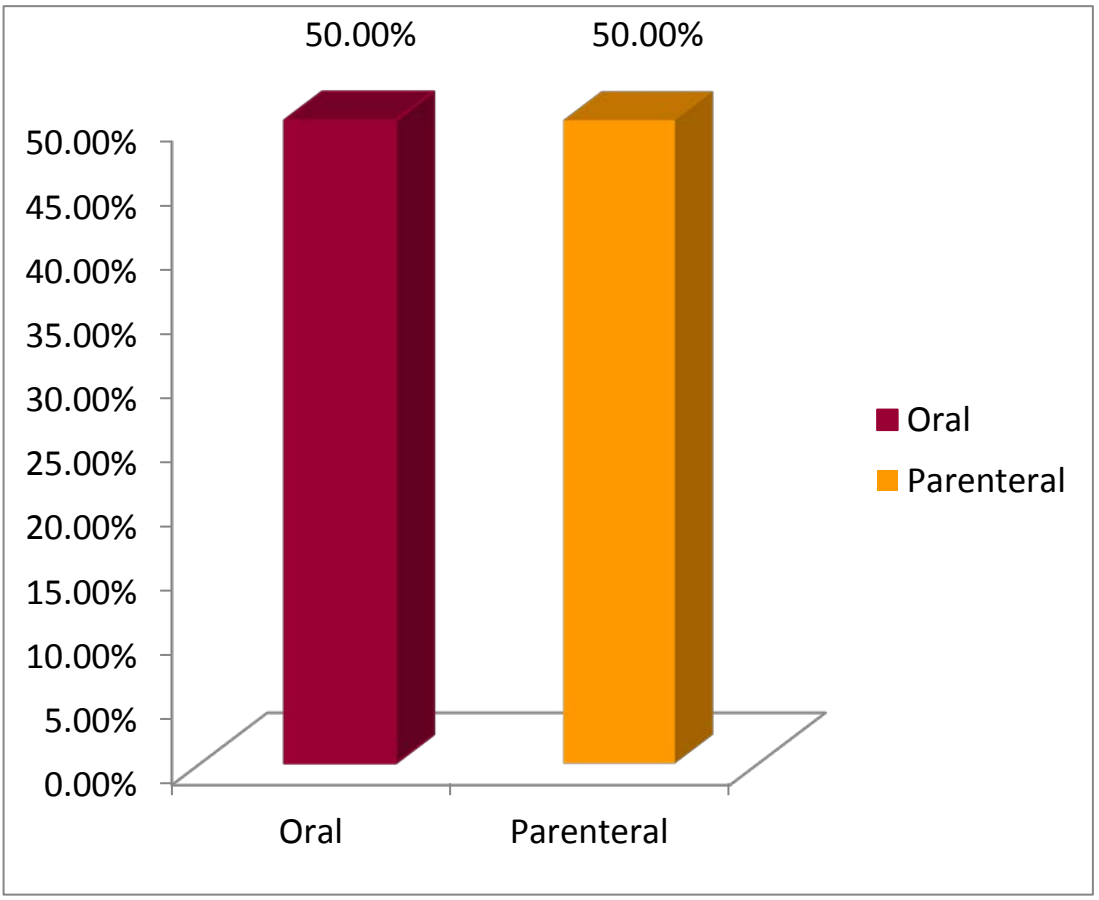


TABLE : 8

FATE OF SUSPECTED DRUGS

Fate of suspected drug	Number	Percentage
Drug withdrawn	**5**	**41.66%**
Dose altered	**4**	**33.33%**
No change	**3**	**25.00%**

REPORT:

In 5 (41.66%) cases the suspected drug was withdrawn while no change was made with suspected drug in 3 (25.00%) and the dose was altered in 4 (13.33%) cases.

FIGURE : 8

FATE OF SUSPECTED DRUGS

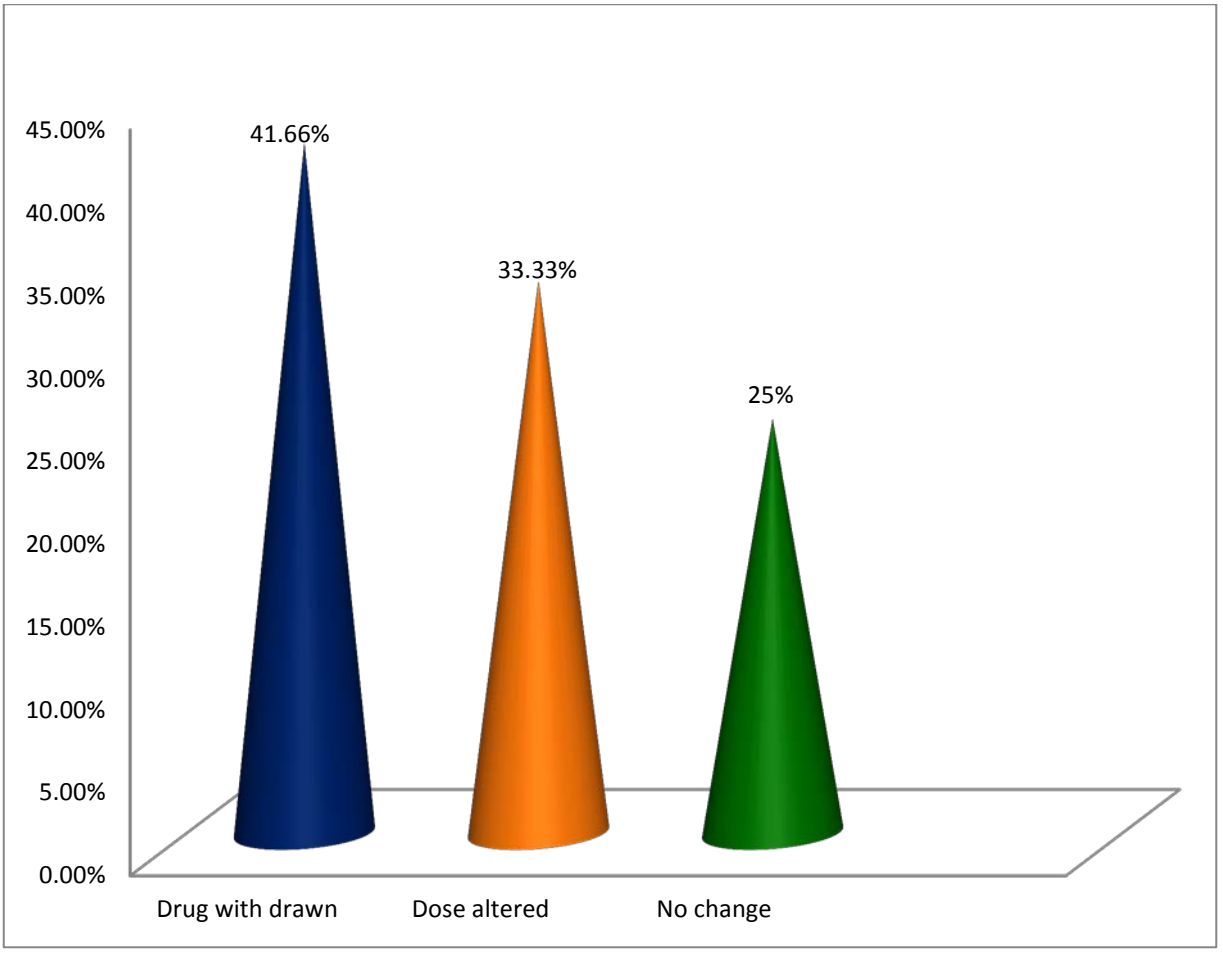


TABLE : 9

OUTCOME OF ADRs

Management of ADRs	Number	Percentage
Recovered	**11**	**91.66%**
Fatal	**0**	**0%**
Unknown	**1**	**8.34%**

REPORT:

Out of 12 reported ADRs, 11 (91.66%) patients recovered, and there is no fatal ADRs, 1 (8.34%) cases were found to be unknown.

FIGURE : 9

OUTCOME OF ADRs

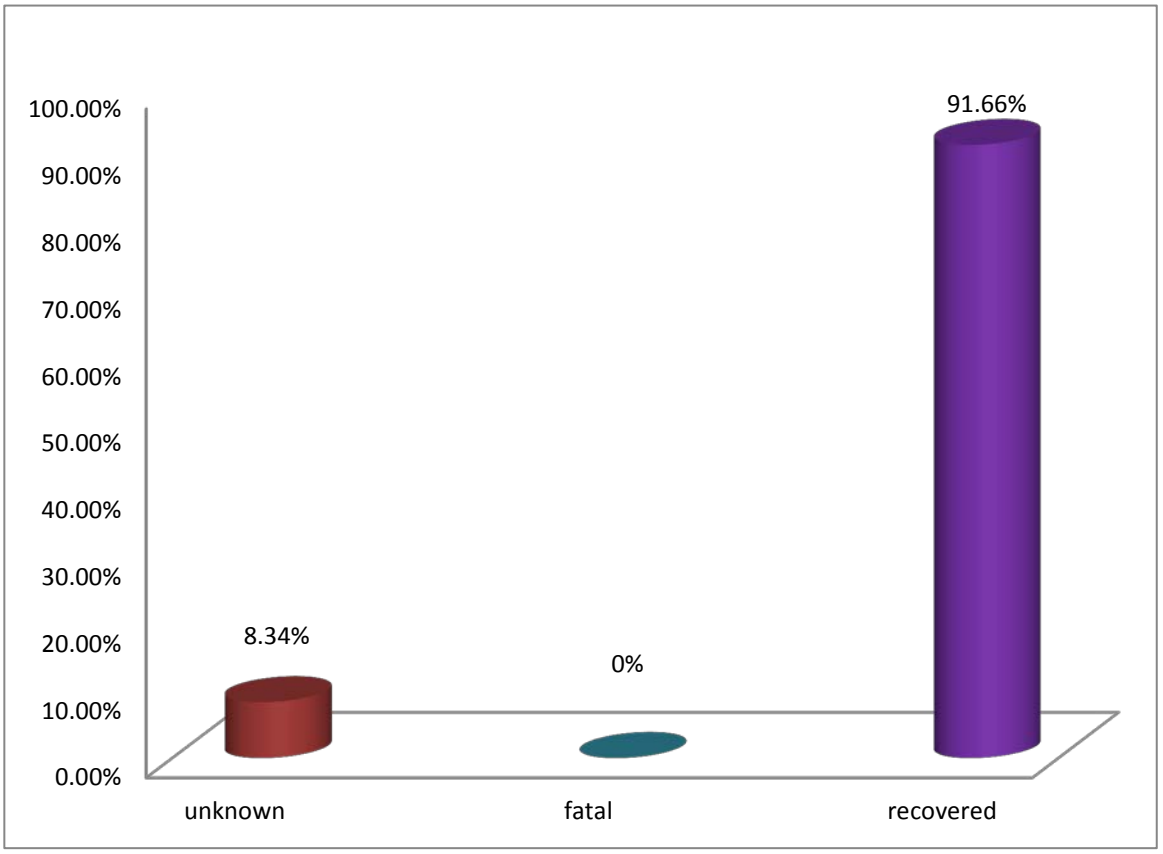


TABLE : 10

TREATMENT GIVEN

Treatment given	Number	Percentage
Specific	**2**	**16.66%**
Symptomatic	**9**	**75.00%**
Nil	**1**	**8.33%**

REPORT:

Specific treatment was given in 2 (16.66%) cases while 9 (75.00%) cases required symptomatic treatment and no treatment was given for 1 (8.33%) cases.

FIGURE : 10

TREATMENT GIVEN

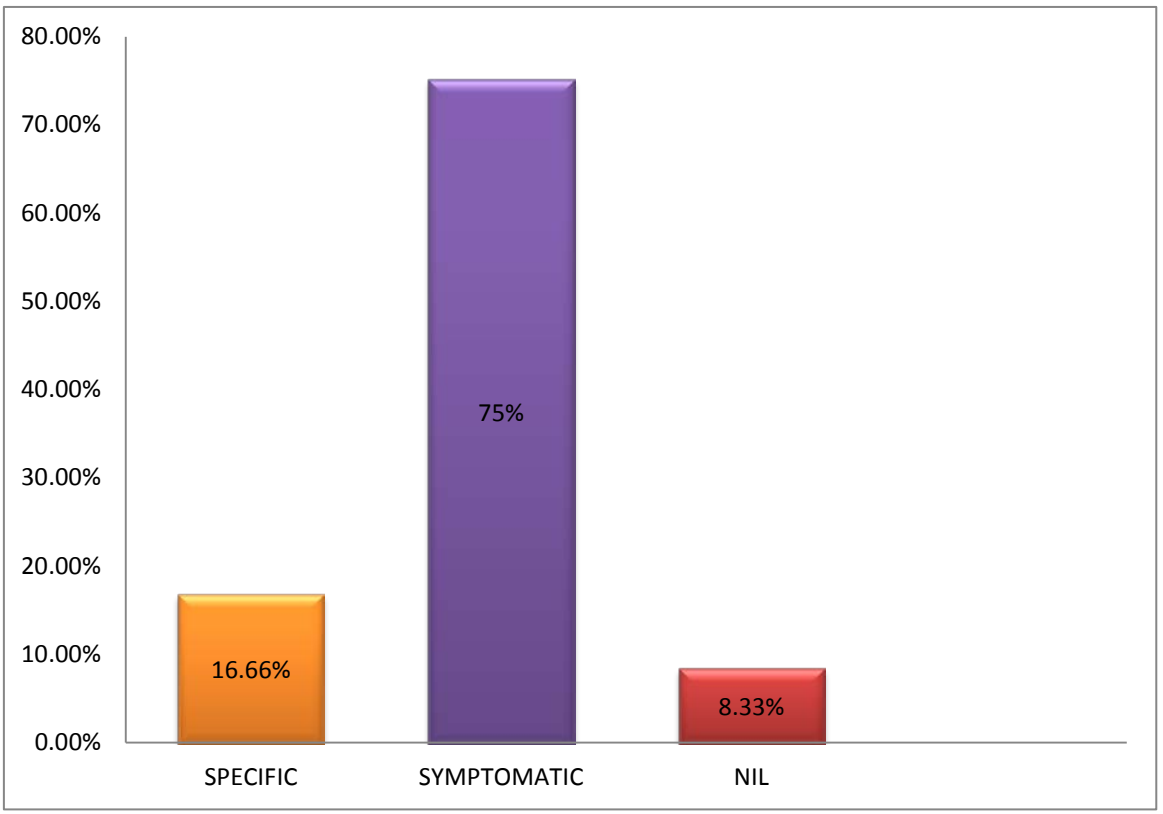


TABLE : 11

LEVEL OF SEVERITY OF REPORTED ARDs

(USING MODIFIED HART WIG AND SIEGEL SCALE)

Severity	Number	Percentage
Mild	**4**	**33.34%**
Moderate	**8**	**66.66%**
Sever	**0**	**0%**

REPORT:

Moderate reactions accounted for 8 (66.66%) followed by mild 4 (33.33%) and no reactions were found to be severe.

FIGURE : 11

LEVEL OF SEVERITY OF REPORTED ARDs

(USING MODIFIED HART WIG AND SIEGEL SCALE)

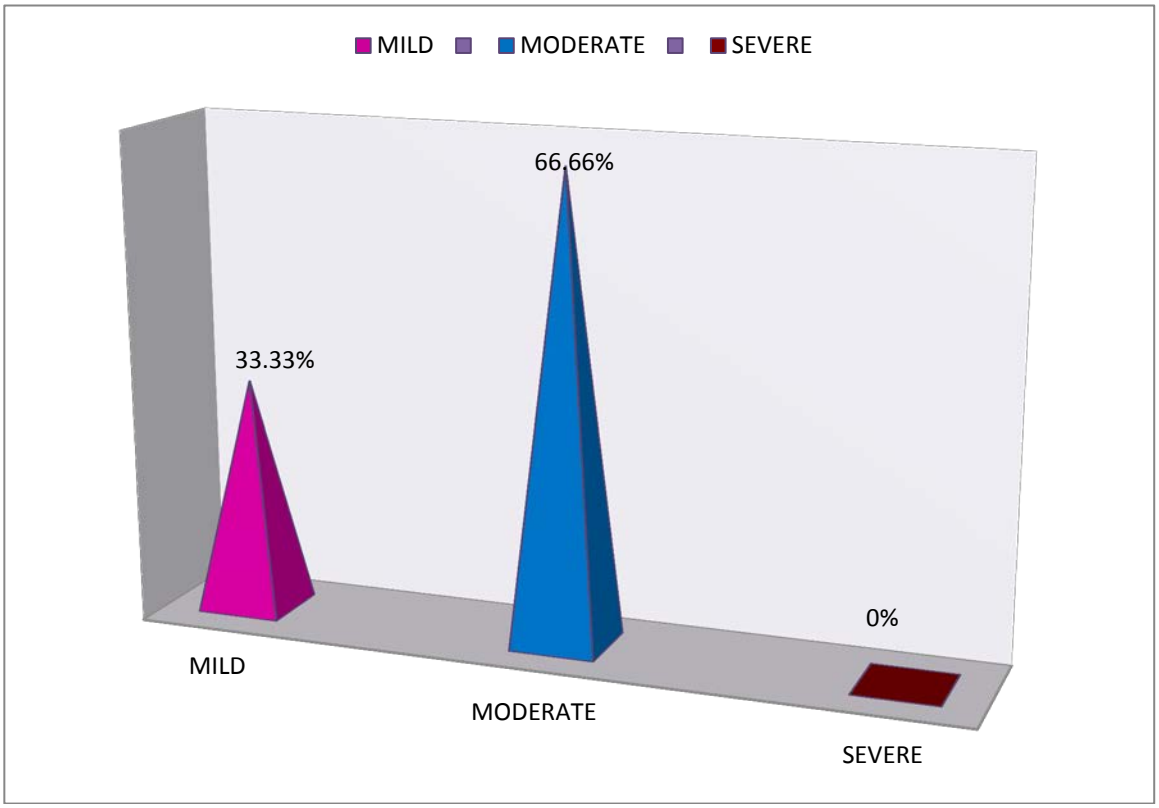


TABLE : 12

CAUSALITY ASSESSMENT OF ADRs

(USING NARANJO SCALE)

	Number	**Percentage**
Definite	0	**0%**
Probable	6	**6.25%**
Possible	57	**59.37%**
Unlikely	37	**38.54%**

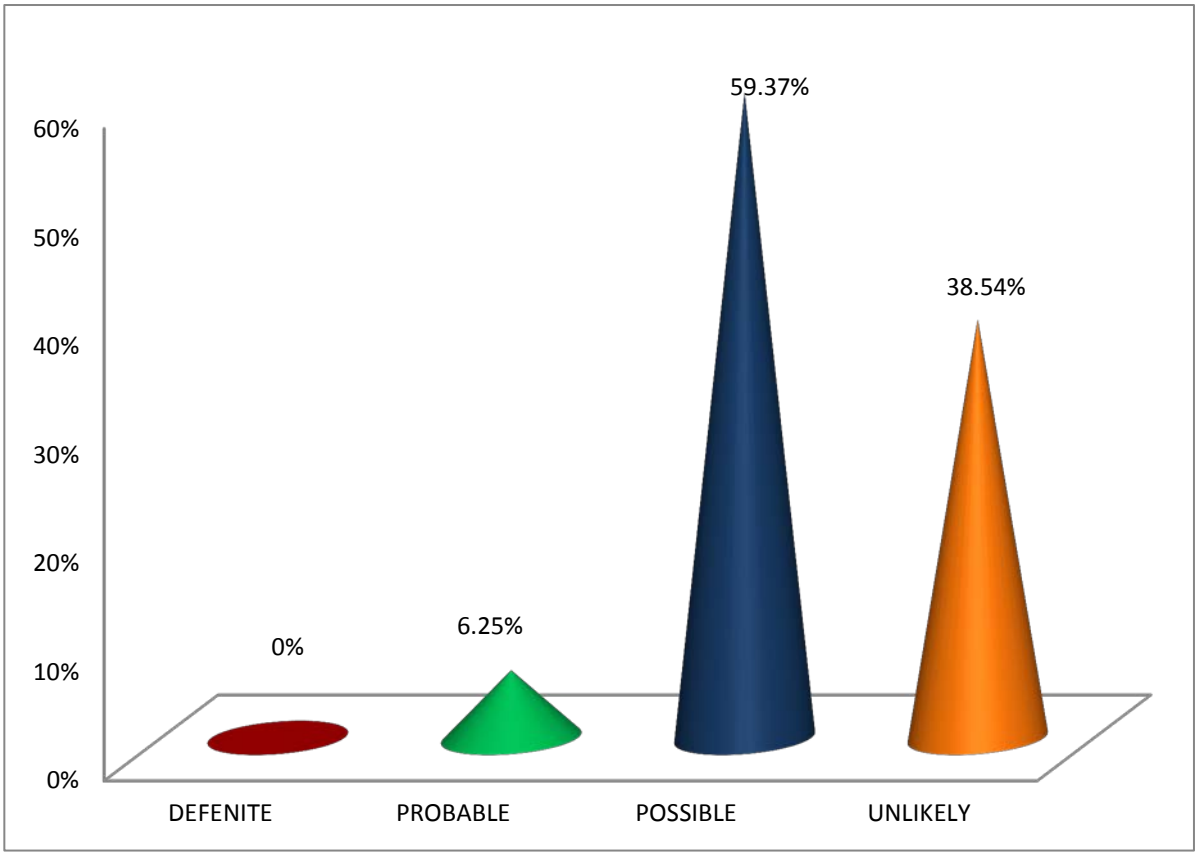
REPORT:

Using Naranjo scale for causality assessment 6 (6.25%) was probable,57 (59.37%) were possible, 0% definite, and 37 (38.54%) were unlikely.

FIGURE : 12

CAUSALITY ASSESSMENT OF ADRs

(USING NARANJO SCALE)



RESULT

During the study period, a total of 12 adverse reactions of anti infective agents were reported among paediatric patients aged between 1 to 10 years among 100 peadiatric inpatients; The incidence rate of antibiotic adverse reactions was found to be 12%.And about 5 (41.66%) male paediatric patients predominated over female 7 (58.34%) in ADR occurrence. This study was a prospective spontaneous reporting study , in which 7 ADRs were reported by active methods and 5 were by passive methods (reported by doctors).Results revealed that GIT 7 (58.33%) was the most affected organ system by adverse reactions due to antibiotics followed by skin 3 (25.00%).The Antibiotic class mostly affected with ADR in paediatric inpatients was pencillins 5 (41.66%) followed by cephalosporin 2 (16.66%).Of the reported ADRs, Type A 10 (83.33%) was most common compared to type B 2 (16.66%) reactions according to the ADR classification by Rawlin and Thomson.

In 5 (41.66%) cases the suspected drug was withdrawn while no change was made with the suspected drug in 3(25.00%) and the dose was altered in 4 (33.33%) cases. From this study, it was found out that there was recovery from ADRs in a total of 11(91.66%) patients although 0% had fatal ADRs. Out of this 1 (8.34%) case was found to be unknown. Specific treatment was given in 2 (16.66%) while 9 (75.00%) cases required symptomatic treatment.

As per Naranjo scale 6 (6.25%) were probable, 57(59.37%) were possible, 0% were definite and 37(38.54%) were unlikely. Of the reported ADRs moderate reactions accounted for 8 (66.66%) followed by mild 4 (38.34%) and no reactions were found to be severe.

DISCUSSION

DISCUSSION

Antibiotics are used for treatment and prophylaxis of various infectious conditions and are considered as safer drugs when used rationally. But, like other drugs, they also show some adverse reactions in various patient conditions. In the studies carried out in Nigerian children and R. Priyadharsini et al. antibiotics are the most accounted drug class in ADR occurrence. Infants and very young children are at high risk of developing ADRs than adults because their capacity to metabolize drugs is not fully developed.

In this study, predominance of male sex for adverse drug reactions may be due to majority of the admitted paediatric patients were male with more antibiotic use during the study period. The study conducted by Jimmy Jose et al. and Suthar J.V and Desai S.V also showed male predominance, where as two other studies by G .Starveva et al. and M.M Hussain et al. showed female predominance.

More number of antibiotic adverse drug reactions were detected in general paediatric medicine department, and may be due to increased use of antibiotics in these departments for treatment and prophylaxis of various diseases. The documented antibiotic adverse drug reactions were mainly affecting GIT and skin and this study also pointed out the same. The study of Benjamin Horen et al. and PJ Annie also found the predominance of gastrointestinal system followed by skin in ADR occurrence.

Analysis of the type of reported ADRs according to Rawlin and Thompson revealed type A predominance. This result is in line with the study conducted by K.A Oshikoya et al. and G. Starveva et al. but in another study by Suthar J.V and Desai S.V, all the reported reactions were type B reactions. Type A reactions are dose related and thus were preventable from their known pharmacology and there for all of them were potentially avoidable.

The analysis of the fate of the suspected drugs showed that the drug was withdrawn in many of the cases and dose altered in some while no change was made with the suspected drug in others, Because of considering the risk benefit ratio in specific patients and in some cases, the use of antibiotics was according to the culture and sensitivity reports. The results revealed that pencillins were the most accounted antibiotic class that cause ADRs in paediatrics. This result is in line with the study of R.Priyadharsini et al. ie, vancomycin and penicillins were most frequent in their study.

CONCLUSION

Adverse drug reactions are one of the drug related problems in the hospital setting and is a challenge for the ensuring drug safety. Antibiotics comprise the major volume of the drug family and inpatient prescriptions, and are the most irrationally prescribed drug class. So that implementation of antibiotic guidelines form the hospital scenario and strict adherence should be ensured to promote their rational use in children. The health system should promote the spontaneous reporting of adverse drug reactions, proper documentation and periodic reporting to regional pharmacovigilance centers to ensure drug safety.

The most commonly prescribed drugs are those most often implicated in ADRs in children. Penicillins, cephalosporins, aminoglycosides etc. are the commonly prescribed class of anti-infective agents in paediatric department, during the study period. The antibiotic class mostly affected with ADRs was found to be penicillins followed by cephalosporins.

The study concluded that spontaneous reporting of Adverse Drug Reaction is farely good in our hospital setting. ADRs may increase costs of patient care and may mimic disease, resulting in unnecessary investigations and delay in treatment. Active involvement of a well trained clinical pharmacist for detecting the Adverse Drug Reaction and delivering the awareness classes for the healthcare professionals regarding the need of reporting ADRs, particularly those that are serious or rare.

ANNEXURE

ANNEXURE NO: 1 NARANJO SCALE

Patient Name: **Sex:** **Age:** **I.P No:** **Dept:** **Consultant:**

S.NO	QUESTIONS	YES	NO	N.K	SCORE
1	Are there previous conclusive reports on this reaction?				
2.	Did the adverse event appear after the suspected drug was administered?				
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?				
4	Did the adverse drug reaction reappear when the drug was read ministered?				
5	Are there alternative causes (other than the drug) that could solely have caused the reaction?				
6	Did the reaction reappear when a placebo was given?				
7	Was the drug detected in the blood (or other fluids) in concentration known to be toxic?				
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?				
9	Did the patient have a similar reaction to the same drug or similar drugs in any previous exposure?				
10	Was the adverse event confirmed by any objective evidence?				

ANNEXURE NO:6 ADVERSE DRUG REACTION REPORTING & DOCUMENTATION FORM

C.G.M HEALTH CARE S.S.V HOSPITAL PUNALUR

ADVERSE DRUG REACTION REPORTING & DOCUMENTATION FORM

Patient Information

Patient Name: I.P. No./O.P. No:
Age: Dept/Unit:
Sex: ☐M ☐F Consultant:
Weight:

Reason for Admission Diagnosis

.....
.....

Suspected adverse reaction Date of onset

.....
.....
.....

Date of Recovery

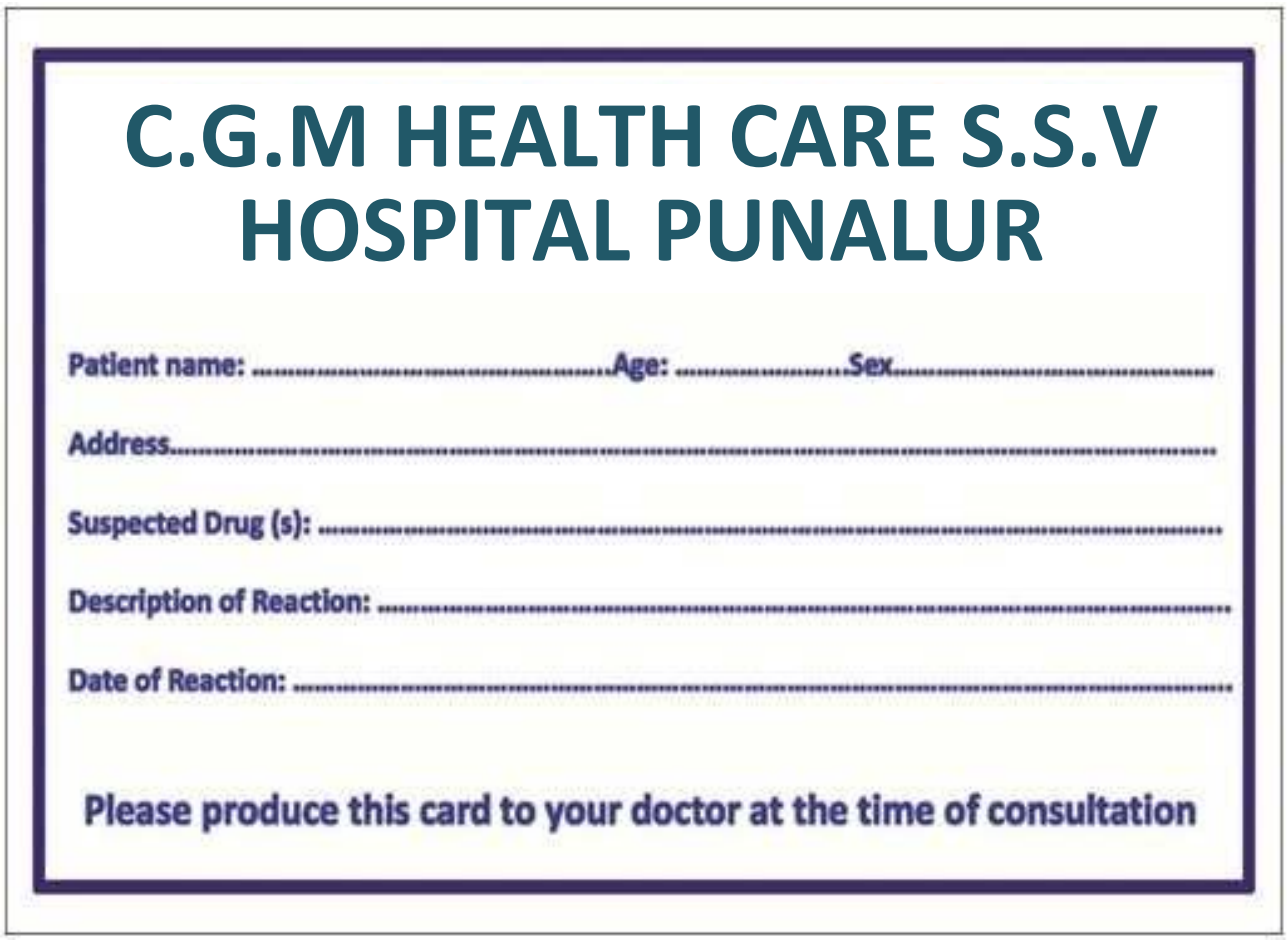
.....

Drugs used Prior To Reaction	Dose	Route & Frequency	Date Started	Date Stopped	Reason for use

Suspected drug

Class of Drug	Labelled Strength	Manufacturer	Brand Name	Batch/lot	Expiry date

ANNEXURE NO: 5 ALERT CARD



ANNEXURE NO : 7

SCALES FOR DETERMININING SEVERITY, PREDICTABILITY & PREVENTABILITY OF ADR

ADR SEVERITY ASSESSMENT SCALE

(Modified Hart wig and Siegel)

- **Mild:**

Level 1: The ADR requires no change in treatment with suspected drug. Or

Level 2: The ADR requires that the suspected drug be withheld, discontinued, or otherwise changed. No antidote or other treatment is required, and there is no increase in length of stay.

- **Moderate:**

Level 3: The ADR requires that the suspected drug be withheld, discontinued otherwise changed, and or an antidote or other treatment is required. There is no increase in length of stay.

Or

Level 4(a): Any level 3 ADR that increases length of stay by at least one day. Or

Level 4(b): The ADR is the reason for Admission.

- **Severe:**

Level 5: Any level 4 ADR that requires intensive medical care.

Or

Level 6: The ADR causes permanent harm to the patient.

Or

Level 7: The ADR either directly or indirectly leads to death of the patient.

PATIENT CONSENT FORM

I.....exercising my power of choice hereby give my consent to be included in the study on "A prospective Study of adverse drug reaction of anti infective agents in paediatric patients" conducted by Bino Babu, Post graduate student in C.G.M Health care sree shanmugha vilasam Hospital , Punalur, Kollam

The principal investigator had informed me about the complete description of the study

I whole heartedly without any compulsion agree to give all the relevant data regarding the study.

I am aware of to opt out this study at any given time without hindrance.

I will not be subjected to any harmful tests as a part of this study

I need not suffer any economic liabilities for this study.

Date

Name of the Patient/Caregiver

Address of Investigator

Bino Babu

2nd Year M.Pharm Student

Ultra College of Pharmacy, Madurai

ANNEXURE NO: 3 ADVERSE DRUG REACTION REPORTING & DOCUMENTATION FORM

C.G.M HEALTH CARE S.S.V HOSPITAL PUNALUR

ADVERSE DRUG REACTION REPORTING & DOCUMENTATION FORM

Patient Information

Patient Name: I.P. No./O.P. No:
Age: Dept/Unit:
Sex: ☐M ☐F Consultant:
Weight:

Reason for Admission Diagnosis

.....
.....

Suspected adverse reaction Date of onset

.....
.....
.....

Date of Recovery

.....

Drugs used Prior To Reaction	Dose	Route & Frequency	Date Started	Date Stopped	Reason for use

Suspected drug

Class of Drug	Labelled Strength	Manufacturer	Brand Name	Batch/lot	Expiry date

ANNEXURE NO: 2 ADVERSE DRUG REACTION REPORTING CARD

C.G.M HEALTH CARE S.S.V HOSPITAL PUNALUR

NOTIFICATION OF A SUSPECTED ADVERSE DRUG REACTION

Patient's Name:.....Age:.....Sex:.....

IP/O.P.No:.....Dept. .....

Suspected drug(s):.....

Date of suspected drug(s)started:.....

Brief description of reaction:.....

.....

.....

Name of the reporting Doctor:.....

Signature:..... Date:.....

ANNEXURE NO: 4 THANK YOU FORM

C.G.M HEALTH CARE S.S.V HOSPITAL PUNALUR

THANK YOU

DATE:

Dear Dr.....

Thank you very much for reporting the suspected Adverse Drug Reaction (ADR).
You have reported:

_____

_____

_____

Our comment:

_____

_____

_____

_____

_____

Once again, we take this opportunity to thank you for your constant support and encouragement in the management of ADRs.

We look forward to your continuous ADR reporting.

WHAT TO REPORT?

REPORT ALL SUSPECTED ADRs

ULTRA COLLEGE OF PHARMACY, MADURAI

TAMILNADU, INDIA

INSTITUTIONAL ETHICS COMMITTEE

Proposal No: UCP/IEC/2012-2013/26 Date: 03.01.2013

This is to Certify that the Research proposal entitled "Prospective study of Adverse drug reaction of Anti infective agents in Paediatric patients". Submitted by BINO BABU M.Pharm., Pharmacy practice II year presented to the committee held on 03.01.2013 for approval. It was reviewed by the committee and was approved to be carried out as per the protocol.

Dr. J.AMBA BHAVANI M.D. (Microbiology)

Head,

Department of Microbiology,

Best Dental Science College,

Madurai.

ERRATA

S.NO	LINE.NO	PAGE.NO	TYPED AS	READ AS

REVIEW OF LITERATURE

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